Does expert opinion match the definition of Lupus Low Disease Activity State? prospective analysis of 500 patients from a Spanish multicentre cohort.

Irene Altabás-González[1,2]; Iñigo Rúa-Figueroa[3]; Francisco Rubiño[3]; Coral Mouriño Rodríguez[1,2]; Iñigo Hernández-Rodríguez[1], Raul Menor Almagro[4]; Esther Uriarte Isacelaya[5]; Eva Tomero Muriel[6]; Tarek C Salman-Monte[7]; Irene Carrión-Barberà[7]; Maria Galindo[8]; Esther M Rodríguez Almaraz[8]; Norman Jiménez[2], Luis Inês[9]; José Maria Pego-Reigosa[1,2]

[1]Complejo Hospitalario Universitario de Vigo, Vigo, Spain; [2]IRIDIS (Investigation in Rheumatology and Immune-Mediated Diseases) Group, Galicia Sur Health Research Institute, Vigo, Spain; [3]Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain; [4]Hospital Universitario de Jerez de la Frontera, Cádiz, Spain; [5]Hospital Universitario de Donostia, San Sebastián, Spain; [6]Hospital Universitario de la Princesa, Madrid, Spain; [7]Hospital del Mar, Barcelona, Spain; [8]Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal

Corresponding author: Irene Altabás-González, MD

Rheumatology Department

Complejo Hospitalario Universitario de Vigo, Galicia Sur Health Research Institute, Vigo (Spain)

Alto do Meixoeiro s/n, 36200 Vigo (Spain)

irene.altabas@gmail.com

Phone: +34 986811111 (Ext. 211375)

FAX: +34 986811173

ORCID: **0000-0002-0797-5391**

ABSTRACT:

Objectives: To apply Lupus Low Disease Activity State (LLDAS) definition within a large cohort of patients and to assess the agreement between the LLDAS and the physician's subjective evaluation of lupus activity.

Methods: A cross-sectional analysis of a prospective multicentre study of Systemic Lupus Erythematosus (SLE) patients. We applied the LLDAS and assessed whether there was agreement with the clinical status according to the physician´s opinion.

Results: 508 patients (92% women; mean age (±SD): 50.4 years (± 13.7)). A total of 304 (62.7%) patients were in LLDAS. According to physician assessment, 430 patients (86,1%) were classified as remission or low activity. Overall agreement between both evaluations was 71.4 % (95% CI: 70.1–70.5%) with a Cohen´s kappa of 0.3 (0.22-0.37). Most cases (96.1%) in LLDAS were classified as remission or low activity by the expert. Of the patients that did not fulfill LLDAS, 126 (70.4%) were classified as having remission/low disease activity. The main reasons for these discrepancies were the presence of new manifestations compared to the previous visit and a SLEDAI 2-K >4, mainly based on serological activity.

Conclusions: Almost two thirds of SLE patients were in LLDAS. There was a fair correlation between LLDAS and the physician's evaluation. This agreement improves for patients fulfilling the LLDAS criteria. The discordance between both at defining lupus low activity, the demonstrated association of LLDAS with better outcomes and the fact that LLDAS is more stringent than physician's opinion imply that we should use the LLDAS as a treat to target goal.

KEY WORDS: Systemic lupus erythematosus, LLDAS, remission, target, Spanish, cohort, multicentre, DORIS, low activity, disease activity.

KEY MESSAGES:

1. Overall agreement between LLDAS and the physician's expert opinion about lupus activity is fair.

2. LLDAS is more stringent than the physician's opinion at defining low SLE activity.

3. Physicians should use the LLDAS as a treat to target goal in clinical practice.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune multisystemic disease that can affect almost any organ or tissue with a wide range of clinical manifestations. The particularities of such a heterogeneous disease renders management in everyday clinical practice extremely difficult. Not only is it important to keep disease activity under control, but also to prevent drug toxicities and damage accrual. Apart from that, morbidity and mortality rates in SLE still remain high [1] despite diagnostic and therapeutic advances in the disease. Therefore, the main groups of experts in the field are looking for new tools such as *treat to target* (T2T) strategies [2], that may improve the outcomes and guide clinicians in the management of this complex disease.

The T2T approach in other rheumatic conditions such as rheumatoid arthritis (RA), spondyloarthritis (SpA) or psoriatic arthritis (PsA) is well established in clinical practice. In RA patients, it has led to a better management of the disease and damage prevention compared to routine control [3]. The main objective of the T2T strategy is to define a specific therapeutic goal, which would be clinical remission or, if that is not possible, low activity of the disease. In the last few years, the definitions of remission in SLE by the DORIS (Definition Of Remission In SLE) taskforce [4] and the Lupus Low Disease Activity State (LLDAS) [5] by the Asia-Pacific Lupus Collaboration (APLC) have emerged with the aim of being implemented as a T2T approach in SLE.

The DORIS taskforce defined remission in 4 different states mainly depending on whether the patient is receiving treatment (apart from antimalarials) or not, and also on whether the patient has serological activity or not. The Safety of Estrogens in Systemic Lupus Erythematosus National Assessment (SELENA)-SLE Disease Activity Index (SLEDAI) physician global assessment (PGA, scale 0–3)) must be <0.5. These four remission states are: complete remission (SLEDAI-2K=0), and clinical remission (clinical SLEDAI-2K=0, hypocomplementemia and presence of anti-dsDNA antibodies are allowed). In these two clinical states, treatments apart from antimalarials are not allowed. The other two remission states are: complete remission on treatment (complete ROT) and clinical remission on treatment (clinical ROT). In these two remission states, treatment with a maximum of 5mg prednisolone per day and immunosuppressive drugs (conventional immunomodulators and biologics) are allowed. More recently, it has been proposed that the most appropriate of these four definitions of remission would be the one that corresponds to clinical ROT [6]. On the other hand, LLDAS is formed by the following criteria: (a) SLEDAI-2K≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, and fever) and no hemolytic anemia or gastrointestinal activity; (b) no new features of lupus disease activity compared to the previous assessment; (c) SELENA-SLEDAI PGA ≤1; (4) current prednisolone (or equivalent) dose ≤7.5mg daily, and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs [5].

These clinical states have been analyzed in other cohorts showing beneficial effects on reducing damage accrual, flares, hospitalizations and better quality of life scores [6-11].

However, the different studies showed that they are difficult to achieve and/or maintain over time [12-16].

The objective of our study is to analyze the agreement between the LLDAS definition and the clinical status of the patient according to the expert opinion of the rheumatologist; and explore modifications of LLDAS definition that may improve it.

Study design

We are carrying out a national, multicentre, longitudinal study in order to evaluate the association of LLDAS with other outcomes such as damage accrual. The study is currently on-going, with data collection taking place once a year over 3 consecutive years, using a standardized electronic case report form. The current study corresponds to the cross-sectional analysis of the baseline data. A specific protocol was created to collect data on around 250 variables per patient. To ensure data homogeneity and quality, every item in the protocol has a highly standardized definition. A previous training course for investigators was carried out to avoid information bias. All investigators had online access to guidelines on how to complete the protocol. Patients were recruited at 7 Spanish Rheumatology Departments. Ethics approval for this study was obtained from the Ethics Committee of Galicia (CEImG). All patients signed an informed consent form prior to participation.

Patients

We included consecutive patients in the outpatient clinical setting. Inclusion criteria were: (a) age of 18 years or older and (b) diagnosis of SLE according to the revised 1997 American College of Rheumatology (ACR) classification criteria or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [17,18]. There were no specific exclusion criteria. To avoid selection bias, patients were recruited homogeneously across Spain. Virtually all patients with SLE treated in our country are referred to hospitals, thus avoiding the possibility of center selection bias.

Variables

At recruitment, demographics, SLE criteria, SLE clinical variables, subjective evaluation of the disease by the rheumatologist and the patient, and data about treatments were collected. Then, most of these variables were collected on a yearly basis. Demographic variables included: gender, date of birth and date of definite SLE diagnosis.

Disease activity in the previous 30 days was measured using SLEDAI-2K [19] and the 28 tender/swollen joint count was also evaluated. Laboratory results of the SLEDAI-2K, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) within 30 days of the visit were also collected. Clinical manifestations of SLE activity not included in the SLEDAI were also measured. Organ damage was assessed by using the SLICC/ACR damage index (SDI) [20].

The expert rheumatologists were asked to categorize patients into five different clinical states: (a) remission; (b) serologically active state; (c) low disease activity; (d) moderate

disease activity and (e) high disease activity. PGA on a scale of 0-3 and patient global assessment on a scale of 0-10 were also captured. Treatment variables included: current use and dose of antimalarials, glucocorticoids, immunosuppressive treatments, and biologic agents.

Disease activity, measured by SLEDAI-2K, of all of the patient visits were compared with the previous one and classified by the expert rheumatologist as: (a) clinically meaningful improvement; (b) no clinically meaningful change in disease activity; and (c) clinically meaningful worsening.

Statistical analysis

Sample size calculation. We calculated the number of patients needed for different levels of agreement, considering that 60% of SLE patients are typically estimated to be in remission or low disease activity and 40% of patients are not. We estimated a sample size of 96 patients to obtain an 80% of statistical power with a significance level of 0.05.

Only the first visit was analyzed for the current study. The data from a first patient visit was compared with the data available in the electronic records from the previous visit. Achievement of remission and LLDAS were obtained according to the predefined criteria. Results were expressed as mean (S.D.) for continuous variables, and as number of patients (percentages) for binary and categorical variables. Expert evaluation of global disease activity was divided into two groups: remission/serologically active clinically quiescent (SACQ)/low activity and moderate/high activity and were compared to the LLDAS definition in a two-by-two table, assessing the agreement between the physician´s expert opinion and the LLDAS definition. Percentage of agreement and Cohen´s kappa was used as measure of agreement between LLDAS and physician evaluation. The percentage of agreement was calculated as the number of agreement scores divided by the total number scores. The Cohen's kappa coefficient (k, is the agreement among the measures other than what would be expected by chance) was used to evaluate the degree of concordance/reliability between the two measures; k <0 is 'no agreement', k=0-0.20 is 'slight agreement', k=0.21-0.40 is 'fair agreement', k=0.41-0.60 is 'moderate agreement', k=0.61-0.80 is 'substantial agreement' and k=0.81-1.0' is 'perfect agreement'[21].

Cases in which there was a disagreement between both evaluations were further analyzed to evaluate which of the LLDAS criteria contributed most to the discrepancy. Then, we carried out a sensitivity analysis, making several changes in the LLDAS criteria, which were modified to check to see if they led to a change in the overall agreement: prednisone doses were adjusted from ≤7.5mg daily to ≤ 5mg daily; SLEDAI-2K ≤4 to clinical (excluding serological activity) SLEDAI-2K ≤4; exclusion of the LLDAS criterion "no new features compared to previous assessment", and finally combining the three of them.

Statistical significance was concluded when $p< 0.05$. All analyses were performed with R Statistical Software, version 4.0.5. (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and disease characteristics

A total of 508 patients were recruited. In this cohort, 92% of patients were female, with mean (±SD) age at diagnosis of 40.7 years (±21) and mean (±SD) disease duration of 10.8 years (±9.9) at the time of recruitment. The mean (±SD) age at recruitment was 50.4 years (±13.7). Previous disease manifestations were determined from the SLICC 2012 criteria on an "ever present" basis. The most common clinical criteria were: arthritis in 69,8% of the patients; cutaneous rash in 62,7 % of the patients and leucopenia in 43,11%. A total of 491 patients (96,65%) were ANA positive, 64,76% had high anti-dsDNA levels and 60,24% had low complement levels. One hundred and sixty-seven patients (31%) had a history of lupus nephritis. At the time of the first visit of the study, the mean (±SD) SLEDAI-2K score was 2.8 (±3.3) and the mean (±SD) SDI score was 0.96 (±1.36). More detailed information about demographics and clinical information of the cohort is depicted in Table 1.

In total, 371 (74%) patients were on antimalarials; 199 (39%) patients were on prednisone, with a mean (±SD) daily dose of 2,5 mg (±5 mg); 219 (44%) patients were receiving conventional immunosuppressants and/or biologics (Supplementary Table S1, available at *Rheumatology* online).

Frequency of LLDAS and remission states

All five criteria for LLDAS were fulfilled in 304 (62.7%) out of the 508 patients. Of the criteria related to the evaluation of disease activity, the most frequently met was the PGA ≤1 in 471 (95.1%) patients. The less frequent one was the SLEDAI-2K≤4, in 462 (80%) patients. On the other hand, of the criteria related to treatments, the glucocorticoid criterion was achieved in 470 (92.5%) patients. More detailed information about the frequency of LLDAS criteria is shown in Table 2.

Clinical remission was achieved in 133 (27.3%) patients, and complete remission in 118 (24.4%) cases. A less stringent definition of remission in which treatment is allowed was met in 267 (54.4%) and 218 (46.4%) cases for clinical ROT and complete ROT, respectively. A total of 267 patients (87,82%) that fulfilled LLDAS criteria also were in clinical ROT.

SLE disease activity according to the expert opinion of the rheumatologist

A total of 430 (86,1%) patients were classified as remission, SACQ or low activity following the assessment of the rheumatologist. Of them, remission was observed in 206 (41,6%), SACQ in 71 (14,3%) and low activity in 153 (30.9%). A total of 55 patients (11.1%) were classified as having moderate activity and 10 (2%) patients as high activity.

Agreement between expert opinion of remission/low activity and LLDAS

The overall agreement between expert opinion of remission/low activity and LLDAS was 71.4% (95% CI: 70.1–70.5%) with a Cohen´s kappa of 0.3 (0.22-0.37) (Figure 1). Most of the cases (96.1%) that fulfilled the definition of LLDAS were classified by the expert as remission, serologically active or low activity. Only 12 (3,9%) patients were classified as moderate or high activity by the expert. Of these 12 patients, three had arthritis, two hypocomplementemia, one myositis, one high anti-dsDNA values, one thrombocytopenia, one rash and one mucosal ulcers. On the other hand, of the patients

that did not fulfill the definition of LLDAS, 126 out of 179 (70.4%) patients were classified by the expert as remission, serologically active or low disease activity (Figure 2). The main reasons for discrepancies in the group that did not fulfill the definition of LLDAS were the presence of new clinical features compared to the previous visit and a SLEDAI-2K score >4, in 74 (58.7%) and 59 (46.8%) patients, respectively. More detailed information about discrepancies is shown in Table 3. We also analyzed the items of SLEDAI-2K exceeding 4 points (Supplementary Table S2, available at *Rheumatology* online).

We adjusted the following criteria of the LLDAS definition to determine if there was a variation in agreement: prednisone dose to 5 mg daily, clinical SLEDAI-2K≤4, exclusion of the criteria "no new features of lupus disease activity compared to previous assessment" and the combination of the three of them. The adjustment that brought about the most significant increase in agreement was the exclusion of the comparative features with the previous visit, with agreement going up from 71.4 % to 82.6% (95% CI: 81.61-83.96%) with a Cohen´s kappa of 0.45 (0.36-0.55). Lowering the cutoff point of prednisone to 5mg/daily dose did not change the level of agreement neither a significant change in the percentage of patients in LLDAS (Table 4).

Discussion

Treating a disease to an objective target state has been applied in the management of several chronic illnesses such as diabetes mellitus, hypertension and hyperlipidemia. This treat to target approach has been implemented later in different rheumatic diseases including RA, PsA or SpA in which the optimal target is generally considered the lowest level of activity achievable (remission or low disease activity) [3,22-23]. This approach, together with tight monitoring and control, have substantially changed the course of these diseases, with better long-term outcomes [24].

In the last few years there has been increased interest in adopting a similar therapeutic strategy for SLE and new concepts of remission and low disease activity have emerged for the disease. The ultimate goal in SLE is long-term survival and the prevention of organ damage with an adequate control of disease activity and a management minimizing the irreversible effects of treatments. Thus, the definition of remission and low disease activity in SLE includes both the activity and treatment domains as well as the expert assessment (scale 0-3) [2,4,5].

The current definition of LLDAS has been validated prospectively and shown to be associated with reduced flare rate and damage accrual in different international SLE cohorts [5,7-9, 15, 25-32]. The protective effect of LLDAS on damage accrual has also been demonstrated in the early stages of SLE in different inception cohorts [8,27,29]. A multicenter study in the UK described that the achievement of LLDAS and remission was also associated with significantly lower risk of severe flare/new damage in childhood SLE [9]. As important as the aforementioned, is the demonstration that achievement of LLDAS is associated with a significant reduction in mortality in SLE patients, including those newly diagnosed [8, 32]. It has also been seen that LLDAS has a favorable impact on other outcome measures such as a better health-related quality of life [30, 32-34], better pregnancy outcomes [35] and reduced direct hospital health care costs [36]. All these associations make LLDAS an useful tool to be used in a real world treat to target setting.

In the first visit of our study, around two thirds of the patients met the LLDAS definition while the different categories of remission were reached in 24.4% to 54.4 %, for complete remission and clinical ROT, respectively. These remission and LLDAS rates are similar to rates previously reported in Europe [25,37]. Although remission is a more ambitious goal, it is more difficult to achieve and maintain over time [16].

In this analysis, we evaluated the agreement of the LLDAS definition with the physician's expert opinion of remission/low activity. We applied the LLDAS definition to our cohort of patients and, at the same time, asked the treating clinician to classify the patient into five different categories (remission, serological activity, low, moderate or high activity). The overall agreement between these two evaluations was fair. Although the agreement in the group in LLDAS was 96%, there was an important percentage of patients that physicians considered in remission or low activity but did not reach LLDAS definition. This can indicate that clinicians may think that patients are in remission/low activity when they are not in LLDAS and therefore are at risk of damage accrual. This finding suggests that clinicians should use LLDAS as a treat to target goal in clinical practice as the LLDAS achievement has been associated with better outcomes.

Further analysis revealed that the main reasons for this disagreement were the presence of new features of lupus disease activity compared to the previous assessment (58.7% of cases), and the non-fulfilment of SLEDAI-2K≤4 (46.7%). Only in 16 (12.7%) of those patients, the reason for the disagreement was the fact that they were taking more than 7.5mg per day of prednisone. One explanation could be that they were receiving more than 7.5mg/day for another reason and that therefore the physician considered the patient in remission or low activity from the point of view of SLE.

When we analyzed in detail the domains of the SLEDAI-2K score of those patients exceeding 4 points, we observed that around two thirds of them had serological activity (positive a-dsDNA antibodies or hypocomplementemia) with another clinical manifestation. This can suggest that physicians do not give the same kind of weight to these serological domains when evaluating low disease activity. On the other hand, it is known that SLEDAI-2K score does not discriminate the severity of a clinical manifestation while the treating physician does. Physicians may not qualify stable persistent clinical manifestations as important forms of disease activity.

On the other hand, based on our findings, we think that serologic findings may play an excessive role in the achievement or not of LLDAS, as frequently active manifestations such as arthritis or mucocutaneous involvement are allowed in LLDAS as long as there is no serological activity, while neither of them is allowed to classify as LLDAS in serologically active patients. Thus, LLDAS is more stringent in serological active than in serologically quiescent patients. In fact, in patients with hypocomplementemia and positive anti-dsDNA, no clinical activity is allowed for LLDAS.

Another important observation is that almost two thirds of the patients that did not fulfill LLDAS, and that the physician considered in remission or low disease activity, had different clinical manifestations compared to a previous assessment. This is explained by the heterogeneity of the disease itself, as it can be present in different clinical forms. On the other hand, we did not establish a minimum period of time to compare visits, so a second visit could have been distant in time with respect to our baseline visit. Thus, when

we analyzed a change in the LLDAS definition by eliminating "no new features of lupus disease activity compared to the previous assessment" leads to an increase in agreement between the LLDAS definition and the physician's opinion. However, further analysis is needed to see how this change in LLDAS definition could affect damage prevention and other outcomes.

The prednisone dose cutoff point of 7,5 mg/daily in the LLDAS definition would be deemed by many to be an unacceptably high maintenance dose to classify a patient as low disease activity as the harmful long-term effects of this therapy, even at low doses, are well-known. We observed that with a modification in the cutoff point of the prednisone dose in LLDAS to 5 mg/daily, does not imply an important change regarding the original definition in our cohort, neither in the percentage of patients fulfilling the LLDAS definition nor in the agreement with the expert rheumatologist's assessment. The daily prednisone dose of 5mg is that included in the DORIS definition of remission and the lowering of the permitted threshold to 5mg might have a significant favorable impact in future damage.

Our study is limited by the cross-sectional design of the first visit. The current study is only the baseline analysis of the cohort and the longitudinal stage of our project will allow us to assess the impact of maintaining remission and LLDAS over time, as well as the impact of maintaining these states according to physician's classification on different long-term outcomes such as damage, hospitalization or quality of life.

In conclusion, we found that LLDAS is a feasible target in the treat to target strategy of management of SLE patients. The overall agreement between LLDAS and the physician's expert opinion about SLE activity is fair, although improves considerably in patients that achieve LLDAS. The main reasons for the discrepancy in patients who do not achieve LLDAS are the appearance of clinical manifestations different from the ones in the previous evaluation and a SLEDAI-2K score >4, mainly based on serological activity. This discrepancy implies a greater number of patients considered in low disease activity by the physician when the patient really is not in LLDAS, so LLDAS is a more stringent tool than the physician's opinion at defining low SLE activity. This suggests we should use LLDAS as a treat to target goal in clinical practice.

Acknowledgements

This study is supported by the FIS/ISCIII-Fondo Europeo de Desarrollo regional (FEDER) (Grant number PI17/01366).

Dr. Altabás-González is supported by ACI /FER (21/CONV/02/1266).

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure Statement: The authors have declared no conflicts of interest.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Jorge AM, Lu N, Zhang Y, Rai SK, Choi HK. Unchanging premature mortality trends in systemic lupus erythematosus: a general population- based study (1999-2014). Rheumatol. 2018; 57:337–344.

2. van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, Lerstrøm K, et al. Treat- to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis 2014;73:958–67.

3. Grigor C, Capell H, Stirling A, McMahon A, Lock P, Vallance R. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single blind randomised con- trolled trial. Lancet. 2004;354:263–9

4. van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis. 2017 Mar;76(3):554-561.

5. Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al. Definition and initial validation of a lupus low disease activity state (LLDAS). Ann Rheum Dis 2016;75:1615–21.

6. Ugarte-Gil MF, Gamboa-Cárdenas RV, Reátegui-Sokolova C, Medina-Chinchón M, Zevallos F, Elera-Fitzcarrald C, Pimentel-Quiroz V, Cucho-Venegas JM, Rodríguez-Bellido Z, Pastor-Asurza CA, Alarcón GS, Perich-Campos R. Better Health-Related Quality of Life in Systemic Lupus Erythematosus Predicted by Low Disease Activity State/Remission: Data From the Peruvian Almenara Lupus Cohort. Arthritis Care Res (Hoboken). 2020 Aug;72(8):1159-1162.

7. Zen M, Iaccarino L, Gatto M, Saccon F, Larosa M, Ghirardello A, 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(1):104-110.

8. Sharma C, Raymond W, Eilertsen G, Nossent J. Association of Achieving Lupus Low Disease Activity State Fifty Percent of the Time With Both Reduced Damage Accrual and Mortality in Patients With Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2020;72(3):447-451.

9. Smith EMD, Tharmaratnam K, Al-Abadi E, Armon K, Bailey K, Brennan M, et al. Attainment of Low Disease Activity and Remission Targets reduces the risk of severe flare and new damage in Childhood Lupus. Rheumatology (Oxford). 2021;11:keab915.

10. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, Catoggio LJ, Drenkard C, Sarano J, Berbotto GA, Borba EF, Sato EI, Tavares Brenol JC, Uribe O, Ramirez Gómez LA, Guibert-Toledano M, Massardo L, Cardiel MH, Silveira LH, Chacón-Diaz R, Alarcón GS, Pons-Estel BA; GLADEL. 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 Dec;76(12):2071-2074.

11. Jesus D, Matos A, Henriques C et al. Derivation and validation of the SLE Disease Activity Score (SLE-DAS): A new SLE continuous measure with high sensitivity for changes in disease activity. Ann Rheum Dis 2018;2000: 1–7.

12. Steiman AJ, Urowitz MB, Ibañez D, Papneja A, Gladman DD. Prolonged clinical remission in patients with systemic lupus erythematosus. J Rheumatol 2014;41:1808–16.

13. Zen M, Iaccarino L, Gatto M, Bettio S, Nalotto L, Ghirardello A, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. Ann Rheum Dis. 2015 Dec;74(12):2117-22.

14. Golder V, Kandane-Rathnayake R, Hoi AY, Huq M, Louthrenoo W, An Y, et al; Asia-Pacific Lupus Collaboration. Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort. Arthritis Res Ther. 2016 Nov 9;18(1):260.

15. Tsang-A-Sjoe MW, Bultink IE, Heslinga M, Voskuyl AE. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. Rheumatology (Oxford). 2017 Jan;56(1):121-128.

16. Wilhelm TR, Magder LS, Petri M. Remission in systemic lupus erythematosus: durable remission is rare. Ann Rheum Dis. 2017 Mar;76(3):547-553.

17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

18. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012 Aug;64(8):2677-86.

19. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29:288–91.

20. Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol 2000;27:373–6.

21. Landis JR ,Koch GG The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

22. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially

psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77(1):3–17.

23. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomized controlled trial. Lancet 2015;386(10012):2489–98.

24. Khanna D, Oh M, Furst DE, Ranganath V, Gold RH, Sharp JT, et al; Western Consortium of Practicing Rheumatologists. Evaluation of the preliminary definitions of minimal disease activity and remission in an early seropositive rheumatoid arthritis cohort. Arthritis Rheum 2007; 57:440–7.

25. Tani C, Vagelli R, Stagnaro C, Carli L, Mosca M. Remission and low disease activity in systemic lupus erythematosus: an achievable goal even with fewer steroids? Real-life data from a monocentric cohort. Lupus Sci Med 2018;5:e000234.

26. 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(11):1790-1795.

27. Floris A, Piga M, Perra D, Chessa E, Congia M, Mathieu A, et al. Treatment Target in Newly Diagnosed Systemic Lupus Erythematosus: The Association of Lupus Low Disease Activity State and Remission With Lower Accrual of Early Damage. Arthritis Care Res (Hoboken). 2020; 72(12):1794-1799.

28. Ugarte-Gil MF, Gamboa-Cardenas RV, Reátegui-Sokolova C, Pimentel-Quiroz VR, Medina M, Elera-Fitzcarrald 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 Sci Med. 2022;9(1):e000616.

29. Piga M, Floris A, Cappellazzo G, Chessa E, Congia M, Mathieu A, Cauli A. Failure to achieve lupus low disease activity state (LLDAS) six months after diagnosis is associated with early damage accrual in Caucasian patients with systemic lupus erythematosus. Arthritis Res Ther. 2017 Nov 10;19(1):247. doi: 10.1186/s13075-017-1451-5. PMID: 29126432; PMCID: PMC5681839.

30. Kang JH, Shin MH, Choi SE, Xu H, Park DJ, Lee SS. Comparison of three different definitions of low disease activity in patients with systemic lupus erythematosus and their prognostic utilities. Rheumatology (Oxford). 2021 Feb 1;60(2):762-766. doi: 10.1093/rheumatology/keaa407. PMID: 32793984.

31. Hao Y, Oon S, Ji L, Gao D, Fan Y, Geng Y, Zhang X, Li G, Morand EF, Nikpour M, Zhang Z. Determinants and protective associations of the lupus low disease activity state in a prospective Chinese cohort. Clin Rheumatol. 2022 Feb;41(2):357-366. doi: 10.1007/s10067-021-05940-z. Epub 2021 Sep 30. PMID: 34595670; PMCID: PMC8782788.

32. Kandane-Rathnayake R, Louthrenoo W, Hoi A, Luo SF, Wu YJ, Chen YH, Cho J, Lateef A, Hamijoyo L, Navarra SV, Zamora L, Sockalingam S, An Y, Li Z, Katsumata Y, Harigai M, Hao Y, Zhang Z, Kikuchi J, Takeuchi T, Basnayake BMDB, Chan M, Ng KPL, Tugnet N, Kumar S, Oon S, Goldblatt F, O'Neill S, Gibson KA, Ohkubo N, Tanaka Y, Bae SC, Lau CS, Nikpour M, Golder V, Morand EF; Asia-Pacific Lupus Collaboration. 'Not at target': prevalence and consequences of inadequate disease control in systemic lupus erythematosus-a multinational observational cohort study. Arthritis Res Ther. 2022 Mar 14;24(1):70. doi: 10.1186/s13075-022-02756-3. PMID: 35287720; PMCID: PMC8919535.

33. Golder V, Kandane-Rathnayake R, Hoi AY, Huq M, Louthrenoo W, An Y, Li ZG, Luo SF, Sockalingam S, Lau CS, Mok MY, Lateef A, Franklyn K, Morton S, Navarra ST, Zamora L, Wu YJ, Hamijoyo L, Chan M, O'Neill S, Goldblatt F, Nikpour M, Morand EF; Asia-Pacific Lupus Collaboration. Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. Arthritis Res Ther. 2017 Mar 20;19(1):62. doi: 10.1186/s13075-017-1256-6. PMID: 28320433; PMCID: PMC5359963.

34. Emamikia S, Oon S, Gomez A, Lindblom J, Borg A, Enman Y, Morand E, Grannas D, van Vollenhoven RF, Nikpour M, Parodis I. Impact of remission and low disease activity on health-related quality of life in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2022 Mar 18:keac185. doi: 10.1093/rheumatology/keac185. Epub ahead of print. PMID: 35302581.

35. Kim JW, Jung JY, Kim HA, Yang JI, Kwak DW, Suh CH. Lupus Low Disease Activity State Achievement Is Important for Reducing Adverse Outcomes in Pregnant Patients With Systemic Lupus Erythematosus. J Rheumatol. 2021 May;48(5):707-716. doi: 10.3899/jrheum.200802. Epub 2020 Oct 15. PMID: 33060317

36. Yeo AL, Koelmeyer R, Kandane-Rathnayake R, Golder V, Hoi A, Huq M, Hammond E, Nab H, Nikpour M, Morand EF. Lupus Low Disease Activity State and Reduced Direct Health Care Costs in Patients With Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2020 Sep;72(9):1289-1295. doi: 10.1002/acr.24023. PMID: 31282076.

37. Mucke J, Düsing C, Klose N, Schneider M, Chehab G. Remission in SLE-do DORIS criteria match the treating physician's judgment? A cross-sectional study to assess reasons for discordance. *Rheumatology (Oxford, England)* vol. 60,9 (2021): 4298-4305

Table 1. Demographics and clinical characteristics of the cohort

	Number (%) or mean (± SD) (n = 508 patients)
Female gender	460 (92%)
Age at diagnosis (years)	40.7 (± 21.0)
Disease duration at enrollment (years)	10,8 (± 9.9)
Age at enrollment (years)	50.4 (± 13.7)
SLICC 2012 criteria (ever present)	
Clinical criteria	
Acute cutaneous lupus	262 (51,57%)
Chronic cutaneous lupus	57 (11,22%)
Oral or nasal ulcers	171 (33,66%)
Non-scaring alopecia	156 (30,71%)
Arthritis	355 (69,88%)
Serositis	96 (18,9%)
Renal	158 (31,1%)
Neurologic	32 (6,3%)
Hemolytic anemia	29 (5,7%)
Leukopenia	219 (43,11%)
Thrombocytopenia	88 (17.3%)
Immunological criteria	
ANA	489 (96.26%)
Anti-dsDNA antibodies	329 (64,76%)
Anti-Sm antibodies	95 (18,7%)
Anti-phospholipid antibodies	163 (32,09%)
Low complement levels	306 (60,24%)
Number of SLICC criteria for SLE	6.2 (±2.2)
SLEDAI-2K score at enrollment	2.8 (±3.3)
SLICC/ACR-DI score at enrollment	0.96 (±1.4)
Damage present at enrollment	253 (49.8%)
Clinical SLEDAI-2 K	1.6 ((±2.7)
Current hypocomplementemia	152 (29.9%)
Current elevated a-dsDNA	125 (24.6%)
PGA at enrollment	0.2 (0.49)

ANA: antinuclear antibodies; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics; SLEDAI; systemic lupus erythematosus disease activity index; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; a-dsDNA: anti-double stranded DNA antibodies; PGA: physician global assessment.

Table 2. Frequency of Lupus low disease activity state (LLDAS)and its items

Descriptors of disease activity	Number (%) (n = 508)
1.SLEDAI-2 K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anemia, fever) and no gastrointestinal activity	462 (80.0%)
2.No new features of lupus disease activity compared to the previous assessment	410 (83%)
3. PGA (scale 0–3) ≤1	451 (95.1%)
Immunosuppressive medications	
4. Current prednisolone (or equivalent) dose ≤7.5 mg daily	470 (92.5%)
5. Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs	508 (100%)
All 5 criteria present	304 (62.7%)

SLEDAI: systemic lupus erythematosus disease activity index; PGA: physician global assessment.

Table 3. Reason of disagreement between patients that did not fulfill LLDAS definition and physician assessment as remission or low disease activity.

Descriptors of disease activity	Not achievement of LLDAS Number (%) n=126 (100%)
1.SLEDAI-2 K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anemia, fever) and no gastrointestinal activity	59 (46.8%)
2.No new features of lupus disease activity compared to the previous assessment	74 (58.7%)
3. PGA (scale 0–3) ≤1	4 (3.3%)
Immunosuppressive medications	
4. Current prednisolone (or equivalent) dose ≤7.5 mg daily	16 (12.7%)
5. Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs	

SLEDAI: systemic lupus erythematosus; CNS: central nervous system; PGA: physician global assessment.

Table 4. Agreement between expert opinion of remission/low activity and LLDAS or modified LLDAS.

	Agreement % (95% CI)	Cohen´s kappa
LLDAS original definition	71.4 % (70.17–70.54)	0.3 (0.22-0.37)
LLDAS modified (a) cSLEDAI-2K ≤ 4 excluding serology	74.2% (72.34-75.66)	0.23 (0.18-0.36)
LLDAS modified (b) prednisone ≤ 5 mg	70.3% (68.75-72.04)	0.29 (0.21-0.36)
LLDAS modified (c): excluding "no new clinical features compared to previous"	82.6 % (81.38-83.96)	0.45 (0.36-0.55)
LLDAS modified (a), (b) and (c)	80.75% (79.14-82.29)	0.42 (0.33-0.51)

LLDAS: Lupus Low Disease Activity State; SLEDAI: systemic lupus erythematosus disease activity index.

Figure 1. Agreement between LLDAS and physician classification as remission-low disease activity.

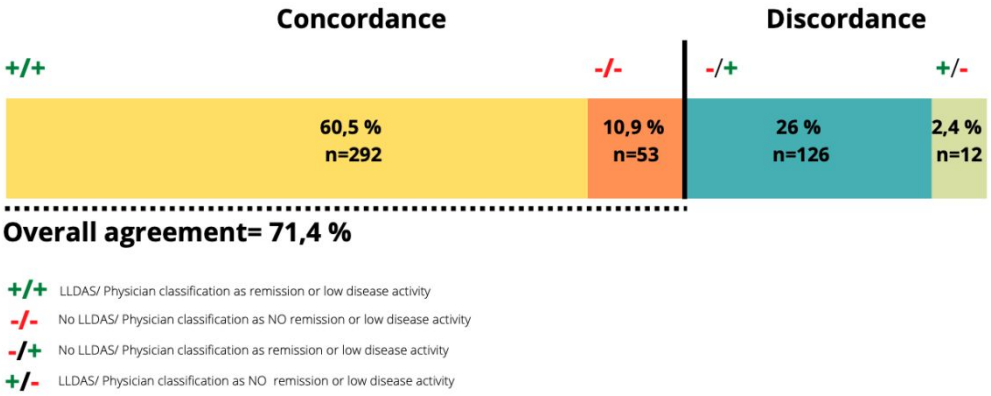
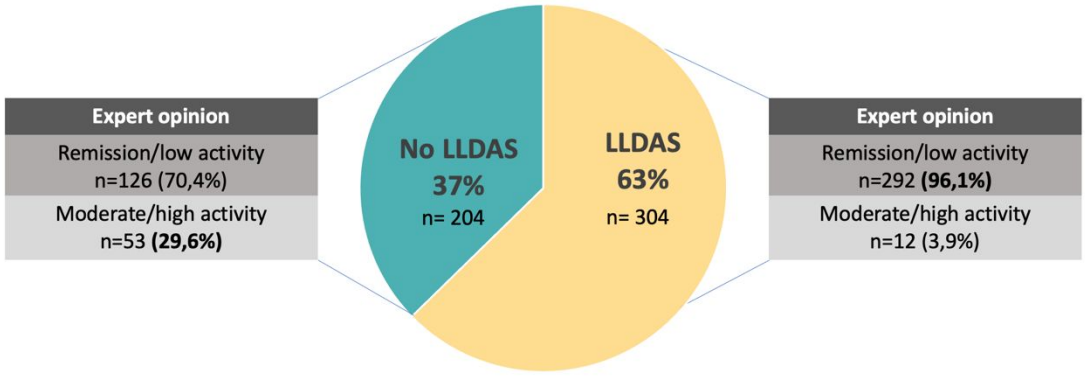


Figure 2. Comparison of LLDAS and expert opinion



LLDAS, Lupus Low Disease Activity State.