Treatment target in newly diagnosed SLE patients: low disease activity and remission are independently associated with lower accrual of early damage.

Short title: LLDAS and remission in early SLE

Authors: Dr. Alberto Floris*, Dr. Matteo Piga*, Dr. Daniela Perra, Dr. Elisabetta Chessa, Dr. Mattia Congia, Prof. Alessandro Mathieu, Prof. Alberto Cauli

Dr Alberto Floris and *Dr Matteo Piga contributed equally to this work.

Affiliation: Chair of Rheumatology and Rheumatology Unit, University Clinic and AOU of Cagliari, Italy.

Grant or other financial supporter of the study: none.

Corresponding author:

Dr Matteo Piga, MD

Chair of Rheumatology and Rheumatology Unit

University Clinic AOU of Cagliari

SS 554 – 09042 - Monserrato (CA), Italy

Phone: +39 (0)70 – 675.4069

Fax: +39(0)70 - 513157

E-mail address: matteopiga@unica.it

Word count: 1869

Conflict of interest: the authors have declared no conflicts of interest.

ABSTRACT

Objectives. To compare the effect of achievement and maintenance of lupus low disease activity state (LLDAS) and clinical remission (CR) in preventing early damage accrual in the early stage of systemic lupus erythematosus (SLE) management.

Methods. In a monocentric cohort of 116 newly diagnosed SLE patients, LLDAS and CR achievement at 6 months (T1) after treatment initiation and their maintenance over the next 12 (T2) months were assessed. Early damage was assessed (T2) using the SLICC/damage index. Uni- and multivariate analysis were performed to evaluate the association of LLDAS and CR with early damage.

Results. LLDAS was significantly more attained than CR both at T1 (42.2% vs. 21.6% of patients, $p<0.001$) and T2 (46.6% vs. 31.9%, $p=0.022$). Overlap between persistent LLDAS and persistent CR was observed in 41.7% of cases. On multivariate analysis, achievement of CR (OR 0.1, $p=0.015$) and LLDAS without CR (OR 0.2; $p=0.049$) at T1, as well as younger age at onset (OR 0.9, $p=0.004$), were negatively associated with early damage. Patients who achieved LLDAS at T1 and steadily persisted in this condition until T2 developed significantly less damage compared to those who failed to maintain it during the T1-T2 interval ($p=0.003$), those who achieved it later than T1 ($p<0.001$) or those who had never been in this condition ($p<0.001$).

Conclusions. Although CR is recommended as the primary treatment target in SLE, LLDAS may represent a valid alternative in the early stage of SLE management. LLDAS and CR maintenance should be targeted to prevent damage.

Significance and Innovations:

- Remission is recommended as the primary treatment target in Systemic Lupus Erythematosus (SLE)
- Remission and Lupus low disease activity state (LLDAS) perform differently in early and late disease stage.
- LLDAS may represent a valid alternative in the early stage of SLE management

INTRODUCTION

Early damage in systemic lupus erythematosus (SLE) is associated with further damage accrual and higher mortality rate (1). Development of new tools for classification and diagnosis will allow early recognition of SLE and early targeted intervention that may reduce damage accrual improving long-term outcomes (2).

Recent advances in Treat to Target (T2T) approaches in SLE include definitions of lupus low disease activity state (LLDAS) and clinical remission (CR) to be applied in clinical practice and trials (3,4). Treatment targets have been applied as outcome measures of treatment response, by assessing their achievement at a single time-point after starting treatment (5-7), and as measures of overall disease control over time, by assessing the cumulative time spent on target (8–12). LLDAS and CR, as measures of response, proved to discriminate between treatments in a clinical trial comparing mycophenolate and azathioprine in active non-renal SLE (6). Further, we recently demonstrated that, in newly diagnosed SLE patients, achievement of LLDAS 6 months after starting treatment protects against damage accrual over the following 12 months (5). More evidence is available on LLDAS and CR as measures of overall disease control. Several studies, performed on SLE cohorts at different disease stages, reported that patients spending the majority of follow-up on target develop significantly less damage (8–11). However, it is still unclear whether the protective effect of LLDAS on damage accrual is due to its overlap with CR, that was reported to be high in a long-standing SLE cohort (8). No studies proved whether such targets may perform differently according to disease stages and, therefore, they could be otherwise used as outcome measures of treatment response or as measures of overall disease control over time.

The main aim of this 18 months longitudinal study was to compare the effect of LLDAS and CR achievement at 6 months and their maintenance over the next 12 months in preventing early damage accrual in a cohort of newly diagnosed and newly treated SLE patients.

METHODS

Patients

Retrospective analysis of routinely collected data from patients included in the Cagliari (Italy) SLE cohort (13) between 1 January 2006 and 30 June 2017 was performed. Inclusion criteria were: (a) SLE diagnosed according to the revised 1997 American College of Rheumatology criteria (14); (b) starting the first treatment for SLE at enrolment in the Cagliari cohort; (c) SLE disease activity index 2000 (SLEDAI-2K) ≥6 at baseline; (d) at least quarterly visits during the study interval; and (e) age ≥18 years. Ethical approval was obtained from local Azienda Ospedaliera Universitaria of Cagliari Ethics Committee and all participants gave their written informed consent to participate in this study according to the Declaration of Helsinki.

Outcomes

LLDAS was defined as SLEDAI-2K ≤4 without major organ activity and no new disease activity, physician global assessment (0–3) ≤1, prednisone ≤7.5 mg/day and well-tolerated immunosuppressant dosages (3). According to previous studies (8,9,12), CR was defined as clinical SLEDAI-2K (increased anti-dsDNA and low complement were excluded) equal to 0 and a prednisone dosage ≤5 mg/day in patients untreated or treated with stable immunosuppressants and/or antimalarials. All patients in CR were expected to fulfill also criteria for LLDAS. In order to assess the real protective effect of LLDAS against early damage, regardless of overlap with CR, data of patients

fulfilling criteria for LLDAS but not for CR (LLDAS/no-CR) were separately analyzed. Status of patients not fulfilling criteria for LLDAS nor CR was defined as “active disease”.

Treatment outcomes achievement at 6 months (T1) and their maintenance over the next 12 months (T2) were assessed. At T2, early damage accrual defined by the SLE international collaboration clinics damage index (SDI) was assessed.

Statistical analysis

Treatment outcomes attainability and maintenance and their association with early damage were compared by Chi squared test or Fisher’s exact test, when appropriate. Uni- and multivariate analysis, by logistic regression, were performed to compare baseline features of patients achieving CR versus those who achieved LLDAS/no-CR at T1. To further assess the independent impact of LLDAS and CR in preventing early damage, a logistic regression model was created including: SDI $\geq$1 at T2 as the dependent variable and male gender, age at onset, disease duration, renal involvement, neurologic disorders, use of antimalarial or immunosuppressant drugs, average daily steroids dosage, CR at T1 and LLDAS/no-CR at T1 as independent variables.

Odds-ratio (OR) with 95% confidence interval (CI) were calculated. Statistical significance was set at p value <0.05. MedCalc® statistical software (Mariakerke, Belgium) was used.

RESULTS

Patients

The study cohort consisted of 116 patients, whose 105 (90.5%) were females. At baseline, median (IQR) age was 34.6 years (26.7-44.3), median diagnostic delay 9.6 months (5.8-24.5) and SLEDAI-2k score 10.0 (8.0-15.0). Hydroxychloroquine, immunosuppressants and glucocorticoids were prescribed in 74 (63.8%), 75 (64.7%) and 107 (92.2%) patients, respectively. The median (IQR) prednisone equivalent dosage was 15.0 (5.9-30.0) mg/day.

Further details on baseline features of the study cohort are reported in the supplementary table 1.

LLDAS and CR achievement and maintenance

LLDAS achievement was significantly more frequent than CR both at T1 (42.2% vs. 21.6%, p<0.001) and T2 (46.6% vs. 31.9%, p=0.022), with 51.0% and 68.5% overlap rate respectively (figure 1). As expected, all patients in CR also fulfilled criteria for LLDAS both at T1 and T2.

On multivariate analysis, a significantly higher SLEDAI score (OR: 1.33, 95%CI 1.04-1.71, p 0.022) at baseline was recorded in patients failing to achieve CR at T1. Although an higher dose of prednisone at baseline was recorded in the LLDAS/no-CR compared to the CR group, that was not statistically significant on multivariate analysis (supplementary table 2).

The overlap rate between persistent LLDAS and persistent CR was 41.7%. Out of 24 patients in LLDAS/no-CR at T1, 13 (54.2%) further improved maintaining CR until T2, 5 (20.8%) remained in LLDAS/no-CR and 6 (25.0%) worsened to active disease during follow-up. Out of 25 patients in CR at T1, 15 (60.0%) maintained it until T2, 3 (12.0%) and 7 (28.0%) worsened to LLDAS/no-CR and active disease, respectively, during the follow-up. Finally, 49 (73.1%) out of 67 active patients at T1 were still active at T2, 9 (13.4%) achieved LLDAS/no-CR and 9 (13.4%) attained CR.

Association of LLDAS and CR achievement with early damage

At T2, at least an item of damage (SDI ≥ 1) was recorded in 28 (24.1%) patients. On univariate analysis, both LLDAS (OR 0.20, 95%CI 0.05 to 0.50; p=0.001), CR (OR 0.10, 95%CI 0.01 to 0.77, p=0.007), and LLDAS/no-CR (OR 0.26, 95%CI 0.07 to 0.95, p=0.038) at T1 were associated with lower prevalence of early damage (Figure 2).

On multivariate analysis, CR (OR 0.07, 95%CI 0.01 to 0.59, p=0.015) and LLDAS/no-CR (OR 0.25, 95%CI 0.06 to 0.99, p=0.049) achievement at 6 months, as well as younger age at onset (OR 0.95,

95%CI 0.91 to 0.98, p=0.004), were confirmed to be negatively associated with damage accrual at 18 months.

Association of LLDAS and CR maintenance with early damage

Patients who achieved LLDAS (including those in CR) at 6 months and maintained it until T2 developed significantly less damage (0/36, 0%) than those (4/13, 30.8%; p=0.003) who failed to maintain it during the T1-T2 interval , those (6/18; 33.3%, p <0.001) who achieved it later than T1 and those (18/49, 36.7%; p<0.001) who had never been in LLDAS (Figure 3). No statistically significant differences between the latter three groups were found in terms of association with early damage.

DISCUSSION

Present study firstly provided comparative data on LLDAS and CR as measures of early treatment response and overall disease control in newly diagnosed SLE patients. In this cohort, LLDAS was achieved more frequently than CR both at six (42.2% vs. 21.6%, p<0.001) and 18 months (46.6% vs. 31.9%, p=0.022) after treatment initiation. The only factor independently associated with achieving LLDAS but not CR after 6 months was the higher SLEDAI score at baseline. The overlap rate (41.7%) between steady LLDAS and CR during the 12 months (T1-T2) of follow-up was lower than reported in a cohort (8) of long-standing SLE patients (75.8%, 93.0%, 75.6%, 74.2%, 89.9% of CR in patients steadily in LLDAS for 1, 2, 3, 4 $\geq$ 5 years, respectively) (7). However, an increasing trend in the overlap rate was observed over follow-up (from 51.0% at T1 to 68.5% at T2), suggesting that the overlap between LLDAS and CR increases in the later stage of the disease.

It was also found that achievement of both LLDAS and CR at 6 months was independently associated with less early damage accrual 12 months later. Especially, the real contribution of LLDAS in preventing early damage was confirmed by separately analyzing patients in CR and those in LLDAS but not fulfilling criteria for remission (LLDAS/no-CR). It was further observed that patients achieving LLDAS or CR at 6 months and maintaining such target over the following 12 months developed significantly less damage compared to those who attained the target just at a single time point or never achieved it. This fact may also suggest that a shorter time spent in LLDAS or CR would be required to prevent damage in newly diagnosed SLE patients than reported in long-standing disease (3,8,10,11). Significant differences did not emerge between persistent LLDAS and CR over 12 months in preventing early damage. Similarly, Ugarte-Gil et al (9), in a cohort of early SLE patients, found that greater intervals of time spent in CR, as well as low disease activity but no-CR, were both protective against development of new damage.

The main limitations of the present study were the relatively small sample size and the retrospective design. The lack of observed damage development in patients with persistent LLDAS and CR prevented from further testing, by multivariate analysis, their independent role in protecting against early damage development. Furthermore, the assessment of patients in LLDAS/no-CR as a separate group was acceptable only to prove the effect of LLDAS in preventing damage, excluding the potential contribution of CR overlap. In clinical practice and trials, it is highly preferable that LLDAS and CR are applied as a continuum (i.e. range of LLDAS), wherein patients in remission are included in the larger subset of patients in LDA and these definitions should be “concentric”, as suggested by Morand and Mosca (15), rather than mutually exclusive. Finally, it has to be noted that PGA was not included in the definition of remission. That was in order to allow a more suitable comparison of our data with previous studies that compared LLDAS and remission in SLE (8,9,12). Moreover, inclusion of a threshold of PGA (e.g. PGA <0.5 in a 0-3 scale) would lead to a more

stringent definition of remission, further supporting our finding of a low attainability of this target in the early stage of SLE management.

In conclusion, although remission is recommended as the primary treatment target in SLE, LLDAS may represent a valid alternative in the early stage of disease management, being more attainable and independently associated with lower damage accrual. However, losing the early attained LLDAS and CR may frustrate prevention of damage and, therefore, LLDAS and CR maintenance should be targeted since the first stage of SLE management. Finally, treatment targets seem to perform differently in early than in late disease stage. This should be considered in designing trials aimed to use LLDAS and CR as primary endpoints.

REFERENCES

1. Rahman P, Gladman DD, Urowitz MB, Hallett D, Tam LS. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. Lupus 2001;10:93–6.

2. Mosca M, Costenbader KH, Johnson SR, Lorenzoni V, Sebastiani GD, Hoyer BF, et al. How Do Patients with Newly Diagnosed Systemic Lupus Erythematosus Present? A Multicenter Cohort of Early Systemic Lupus Erythematosus to Inform the Development of New Classification Criteria. Arthritis Rheumatol 2018 published on 23 Jul 2018. doi: 10.1002/art.40674.

3. 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.

4. van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, Askanase A, 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;76:554-561.

5. Piga M, Floris A, Cappellazzo G, Chessa E, Congia M, Mathieu A, et al. 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;19:247.

6. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Mitjavila F, Castro Salomó A, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. Ann Rheum Dis 2017;76:1575–82.

7. Morand EF, Trasieva T, Berglind A, Illei GG, Tummala R. Lupus Low Disease Activity State (LLDAS) attainment discriminates responders in a systemic lupus erythematosus trial: post-hoc analysis of the Phase IIb MUSE trial of anifrolumab. Ann Rheum Dis. 2018;77:706-713.

8. 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;77:104–10.

9. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, Catoggio LJ, Drenkard C, Sarano J, 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.

10. 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.

11. 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;70:1790-1795.

12. Tsang-A-Sjoe MWP, Bultink IEM, Heslinga M, Voskuyl AE. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. Rheumatology 2017;56:121–8.

13. Piga M, Casula L, Perra D, Sanna S, Floris A, Antonelli A, et al. Population-based analysis of hospitalizations in a West-European region revealed major changes in hospital utilization for patients with systemic lupus erythematosus over the period 2001–2012. Lupus 2016;25:28–37.

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

15. Morand EF, Mosca M. Treat to target, remission and low disease activity in SLE. Best Pract Res Clin Rheumatol 2017;31:342–50.

Figure legend:

Figure 1. Prevalence of different disease activity patterns at 6 (T1) and 18 (T2) months after treatment initiation. CR: clinical remission, LLDAS: lupus ow disease activity state (CR + LLDAS/no-CR), LLDAS/no-CR: patients fulfilling criteria for LLDAS but not for CR, Active disease: inadequate disease control (no-LLDAS/no-CR).

Figure 2 Distribution of early damage (SDI ≥1, at eighteen months, T2) according to achievement of different disease activity patterns at six months (T1). CR: clinical remission, LLDAS: lupus low disease activity state, LLDAS/no-CR: patients fulfilling criteria for LLDAS but not for CR, Active disease: inadequate disease activity control (no-LLDAS/no-CR).

Figure 3. Heatmap of disease activity over the T1-T2 interval and prevalence of early damage. CR: clinical remission, LLDAS: lupus low disease activity state (CR + LLDAS/no-CR), LLDAS/no-CR: patients fulfilling criteria for LLDAS but not for CR, Active disease: inadequate disease control (no-LLDAS/no-CR), SDI: SLICC damage index.