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Achieving Lupus Low Disease Activity State (LLDAS-50) is associated with both reduced damage accrual and mortality in patients with Systemic Lupus Erythematosus.

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Abstract

Objectives: To assess the impact of achieving Lupus Low Disease Activity State (LLDAS-50) on damage accrual and mortality in an inception cohort of patients with Systemic Lupus Erythematosus (SLE).

Methods: We used data from the Tromsø Lupus Cohort, a longitudinal population-based study of all SLE patients in the 2 northern-most counties in Norway. LLDAS was defined as a) SLEDAI-2K ≤ 4 , with no activity in major organ systems b) no new features of lupus disease activity c) current prednisolone (or equivalent) dose ≤ 7.5 mg daily, and, d) well tolerated standard maintenance doses of immunosuppressive drugs.

Results: A total of 69 patients (33.5%) spent at least half of their follow up time in LLDAS, thus achieving LLDAS-50, and these patients had both significantly better survival and lower risk of developing severe SDI over time. After correcting for age and sex, LLDAS-50 was associated with a significant reduction in risk of having severe damage (HR 0.37; 95%CI 0.19 – 0.73, $p < 0.01$), and also a reduction in mortality (HR 0.31; 95%CI 0.16 – 0.62, $p < 0.01$).

Conclusions: Our study validates the findings of the inception cohort by demonstrating that achieving LLDAS-50 is associated with a significant reduction in severe damage, but for the first time also demonstrates a reduction in mortality.

Significance and Innovation

- The most significant finding is that for the first time a reduction in mortality has been demonstrated for those patients with SLE who achieve a low disease activity state.
- This study also validates the findings of the inception cohort by showing reduced risk for severe damage for those patients meeting LLDAS-50.

Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune condition of unclear aetiology with wide ranging manifestations. Despite developments in the field, durable remission in SLE is rare; SLE patients still face a threefold increase in mortality when compared to the general population (1). A major cause of morbidity is the cumulative damage due to persistent inflammation and its treatment

(2). Higher levels of organ damage are seen with persistent high disease activity and have a profound impact on a patient's quality of life causing significant levels of disability and unemployment. This has led to a push to develop a treatment strategy that results in minimising disease activity with consequent reduction in organ damage.

Treat-to-target has been defined as “a therapeutic strategy aimed to treat patients to a goal which is capable of improving disease outcome” (3). The target is usually remission or low disease activity, however rates of disease remission in SLE have been poor, regardless of the definition used (4). According to the international taskforce DORIS (Definitions of Remission In SLE), “the treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by specific organ markers” (5). A definition of a Lupus Low Disease Activity State (LLDAS) has recently been put forward by The Asia Pacific Lupus Collaboration (APLC) as a potential treatment target for patients with SLE. A patient is said to be in LLDAS when they meet the following: 1. SLE Disease Activity Index (SLEDAI) -2K \leq 4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; 2. No new features of lupus disease activity compared with the previous assessment; 3. SELENA-SLEDAI physician global assessment (PGA, scale 0–3) \leq 1; 4. Current prednisolone (or equivalent) dose \leq 7.5 mg daily; and, 5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs (6). The construct validity of this LLDAS definition has been tested against expert opinion and has been shown to have high overall agreement (7). The impact of achieving a LLDAS was investigated with prospectively collected dataset. Those patients that spent majority (>50%) of their time in LLDAS had reduced organ damage accrual and severity according to the SLE Damage Index (SDI) as compared to those who did not (6). We assessed the validity of these findings in a Caucasian inception cohort of patients with SLE.

Methods

The Tromsø Lupus Cohort is a longitudinal population-based study of all SLE patients in the two northern-most counties in Norway. The inception cohort included patients seen since 1990 and fulfilling at least 4 ACR criteria (1982 revision and 1997 update) for the classification of SLE (8). SLE patients were seen by attending physicians of the sole rheumatology service in the area, who as a rule saw patients with quiescent disease twice

annually, and patients with concerns and signs of complications were seen more frequently. Every hospital visit was registered in a database with the use of a template that recorded demographics, clinical findings, medication, and laboratory results. For each patient visit, disease activity was quantified with a SLE Disease Activity Index - 2000 (SLEDAI-2K) score, while damage was scored by SDI (9,10). Information was obtained from patients, hospital records and general practitioners, was verified before inclusion in the relevant scoring systems. Disease duration was the time interval from SLE research diagnosis (defined as fulfilling 4 ACR criteria) until last follow-up visit or time of death. The SDI scores were graded ordinally into 3 subgroups, for every patient for each visit during follow-up, with scores of 0 indicating no damage, scores of 1–2 moderate damage, and scores ≥ 3 severe damage (8). LLDAS was defined as stated above (6). The original definition of LLDAS required patients to have a SELENA-SLEDAI PGA (scale 0–3) ≤ 1 ; however this data was not available for our cohort thus it was not used in determining whether the patients were in LLDAS. Patients were excluded if they had less than 2 recorded visits.

We also evaluated the impact of two novel disease activity points, namely LLDAS-30 and LLDAS-70, which were defined as those patients who spent at least 30% of their follow up time in a LDAS (LLDAS-30) and those that spent at least 70% of their follow up time in LDAS (LLDAS-70).

Statistics:

Data are described with frequencies and percentages or with median and interquartile range (IQR). We applied Kaplan Meier survival curves with Cox regression analysis to derive hazard ratios (HR) and 95% confidence intervals (CI) to quantify the association between LLDAS and time dependent outcomes. All calculations were done using IBM SPSS Statistics version 23 with p values (p) < 0.05 as cut off for statistical significance.

Results:

The median age at diagnosis was 34 years with the majority (84%) being female. The median follow-up time was 125 months (IQR 56 – 212 months) during which 3,646 visits were made by 206 patients for a median number of visits of 13 (IQR 7 – 24). Prednisolone and Hydroxychloroquine were the most common drugs used (89% and 59% respectively). Only 11 patients (3.4%) required either Cyclophosphamide or Rituximab. Arthritis and photosensitivity were the most common clinical

manifestations of the ACR (70% and 57% respectively), with a positive Anti-Nuclear Antibody (ANA) the most common laboratory criterion (96%).

At last follow-up, the majority of the patients (58%) had a total SDI of at least 1, with 28% having a final SDI score of 3 or more and 22% of the entire cohort having an increase in their SDI by 3 or more, from baseline (Table 1).

LLDAS of any duration was achieved by 74% of the cohort. The median time that patients spent in LLDAS was 34 months (IQR 0 – 61 months). A total of 69 patients (33.5%) spent at least half of their follow up time in LLDAS, thus achieving LLDAS-50. These patients had significantly better survival and lower risk of developing severe SDI over time (Figure 1 and 2). After correcting for age and sex, LLDAS-50 was associated with a significant reduction in risk of having severe damage (HR 0.37; 95%CI 0.19 – 0.73, $p < 0.01$), and a reduction in mortality (HR 0.31; 95%CI 0.16 – 0.62, $p < 0.01$). In those patients who reached LLDAS-30 ($n=114$) and LLDAS-70 ($n=38$) there was similar protection against mortality, but achieving LLDAS-30 had no impact on severe damage. Further information on the LLDAS 30 and 70 cohorts are provided in the supplementary

Discussion

Due to the lack of a universally accepted definition of remission in SLE, and the difficulty in achieving remission in studies, researchers have been trying to define alternate, more achievable targets to guide therapy in patients with SLE such as the LLDAS (6, 11). An operational definition of LLDAS was provided by Franklyn *et al* who analysed the impact of achieving this in an inception cohort of 191 patients with SLE and noted that those patients who spent greater than 50% of their time in LLDAS had less organ damage than those that did not (6).

The current study demonstrates similar outcomes to the validation cohort with a notable reduction in risk of severe damage (HR 0.37; 95%CI 0.19 – 0.73, $p < 0.01$). In addition, we also noted a significant reduction in age and sex adjusted mortality risk (HR 0.31; 95%CI 0.16 – 0.62, $p < 0.01$) for those patients achieving LLDAS-50 compared to those who did not. We also analysed the impact on damage and mortality for those patients who achieved LLDAS for 30 and 70% of their total follow up duration. Our findings demonstrate that while achieving LLDAS-70 was also associated with a similar reduction in risk of severe damage (HR 0.38; 95%CI 0.16 – 0.93, $p < 0.05$) and mortality (HR 0.25; 95%CI 0.09 – 0.71, $p < 0.01$), even achieving LLDAS-30 resulted in a reduced risk of mortality (HR 0.36, 95%CI 0.20 – 0.65, $p < 0.05$), and a strong trend towards significance in reducing the risk of severe damage (HR 0.57, 95% CI 0.31 – 1.06, $p = 0.08$). The trend of the LLDAS30 towards protection

against damage accrual was similar to Zen *et al*, who found that a minimum of two years of LLDAS over a seven year follow up (approximately equivalent to LLDAS-30) was required to demonstrate a decrease in damage progression (12).

Similar outcomes with regards to the impact on damage accrual have also been replicated in other studies. Tsang *et al* evaluated the impact of achieving LLDAS-50 in a 183-patient cohort also noted a significant reduction in damage accrual with odds ratio of 0.52 (95%CI: 0.28, 0.99, p=0.046) (13). Ugarte-Gil *et al* analysed the impact of achieving LLDAS in the Latin American Lupus Cohort (GLADEL) and also found that achieving LLDAS was associated with a lower risk of new damage (HR 0.66; 95%CI 0.48 to 0.93) (14).

While the impact of LLDAS-50 on damage accrual has been demonstrated, to the best of our knowledge this is the first study to demonstrate an impact on mortality. The validation cohort did not observe any deaths, while the study by Ugarte-Gil *et al* did not note any significant impact on mortality, they conceded that this likely reflects their relatively short duration of follow up (and consequently fewer events) (6,14). Zen *et al* only reported one death in their cohort therefore were unable to evaluate the relationship between LLDAS-50 and mortality (12).

The fact that patients who spent 70% of their time in a LDAS (LLDAS-70) also had a reduction in their risk of severe damage and mortality is a logical extension of the findings of the above LLDAS-50 studies; however, the significant reduction in mortality associated with achieving at least LLDAS-30 is another very interesting finding. One must exercise caution in interpreting these results as there is likely to be a significant dilution of the effect due to inclusion of patients who achieved LLDAS-50 and LLDAS-70 in the LLDAS-30 cohort. This was shown by the fact those patients who spent exactly 30% of their follow up time (n = 5) did not have a significant reduction in mortality.

This study has some limitations. We did not include a PGA (which forms a part of the LLDAS criteria) as this was information was not available at the time this inception cohort was started. However, previous studies have shown excellent correlation between the PGA and SLDEAI, and the fact that our results echo those of previous studies does raise the interesting point as to whether a PGA is required for the calculation of LLDAS (15). The study population was primarily Caucasian, a cohort known to have better outcomes in SLE. Another limitation is the time frame of data collection (from 1990) as definition of SLE and management concepts have changed significantly since then. Due to this being a retrospective observational study, establishment of a causal relationship between disease parameters and outcomes is also difficult.

Conclusion

Our study validates the findings of the inception cohort by demonstrating that achieving LLDAS-50 is associated with a significant reduction in severe damage, but for the first time also demonstrates a reduction in mortality. Thus LLDAS-50 is a practical and achievable surrogate target that is associated with reduced risk of severe damage, mortality and higher quality of life for patients with SLE.

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TABLES**Table 1: Patient characteristics of the study cohort**

	N = 206
Female	173 (84%)
Age years (IQR)	34.5 (24.7 – 47)
Median number of visits (IQR)	13 (7 – 24)
Median disease duration months (IQR)	127 (58 – 213.5)
Mean SLEDAI (std dev)	2.75 (4.67)
Mean cumulative SLEDAI per patient	42.67
Median baseline SLEDAI (IQR)	7 (4-12)
Median final SLEDAI (IQR)	2 (0-8)
Median Baseline SDI (IQR)	0 (0-0)
Median Final SDI (IQR)	1 (0-3)
Death	46 (22%)

Figure 1: Survival analysis for patients achieving LLDAS-50 to those that do not achieve LLDAS-50

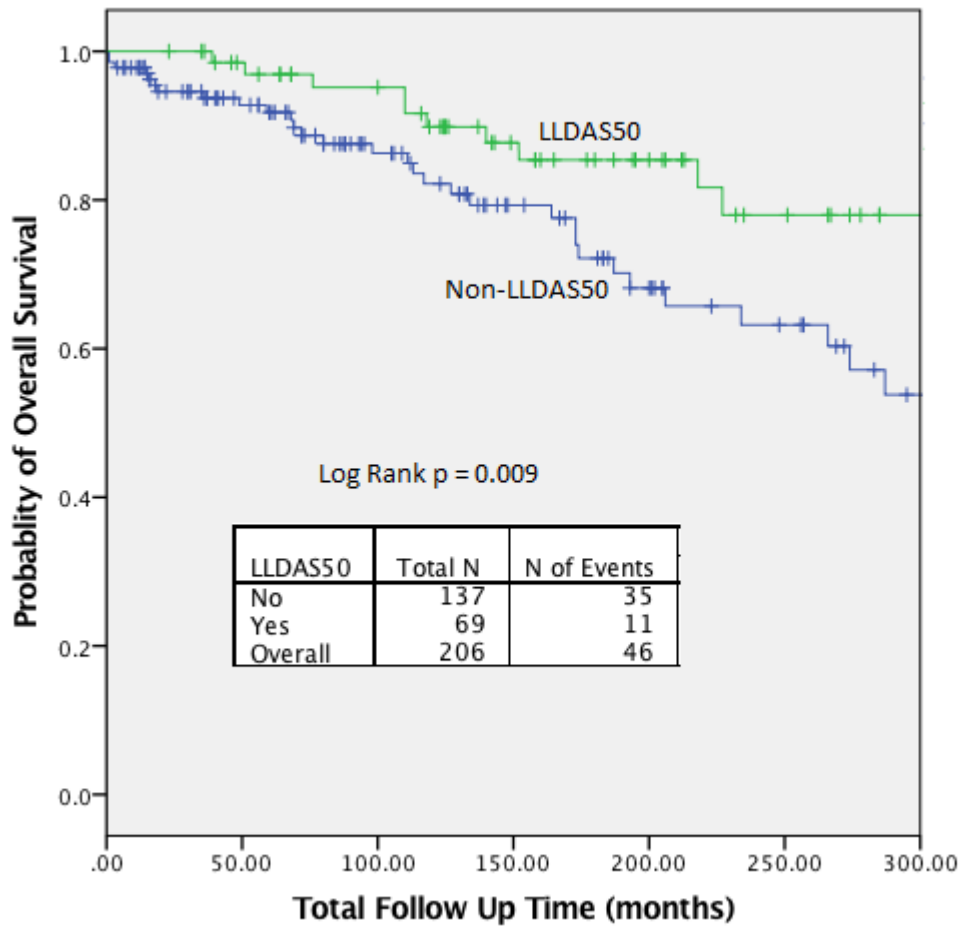
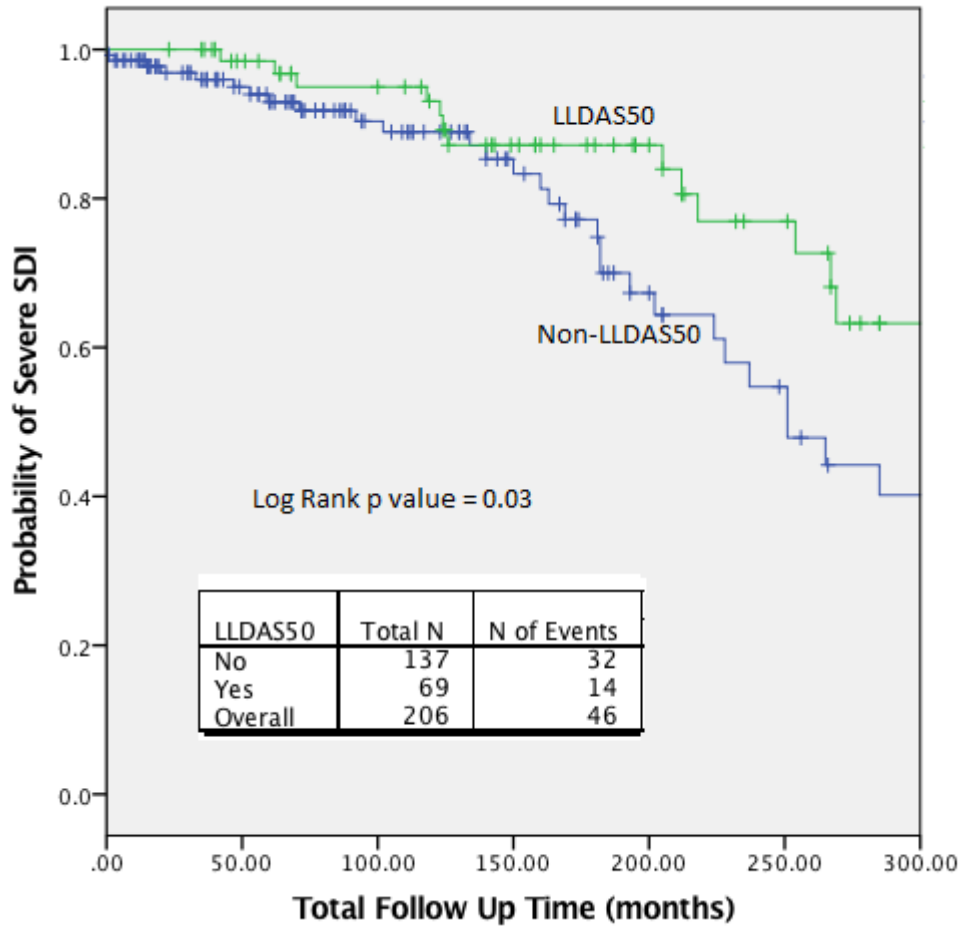


Figure 2: Survival analysis demonstrating the chance of remaining free of severe damage for patients achieving LLDAS-50 to those that do not achieve LLDAS-50



*SDI – Systemic Lupus Erythematosus Damage Index