LLDAS is an attainable treat-to-target goal in childhood-onset SLE

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ABSTRACT

Objectives To study whether clinical remission (CR) and Low Lupus Disease Activity State (LLDAS) are achievable goals in childhood-onset SLE.

Methods Data on medication use and disease activity were prospectively collected. LLDAS was defined as Safety of Estrogen in Lupus Erythematosus National Assessment-SLE disease Activity Index (SELENA-SLEDAI) ≤4 with zero scores for renal, Central Nervous System (CNS), serositis, vasculitis and constitutional components, no increase in any SLEDAI component since the previous visit, PGA ≤1, and prednisone dose ≤7.5 mg/day. CR on treatment (Tx) was defined as a Physician Global Assessment <0.5, SELENA-SLEDAI=0, with prednisone ≤5 mg/day and maintenance treatment with immunosuppressives. CR off Tx was the same but without prednisone or other immunosuppressive usage.

Results 51 patients (700 visits) were included. Within 3 months after diagnosis, 94.1% of children were treated with hydroxychloroquine and 60.8% with prednisone. Prednisone dosage decreased from a median of 0.74 mg/kg/day at diagnosis to 0.44 mg/kg/day at 3 months and 0.16 mg/kg/day at 6 months after diagnosis. Use of mycophenolate mofetil increased from 25.5% to 56.9% within 6 months after diagnosis. All children achieved LLDAS (median 186 days) and 72.5% remained in LLDAS within 6 months after diagnosis. Use of immunosuppressive usage. CR off Tx was the same but without prednisone or other immunosuppressive usage.

Conclusions LLDAS is an achievable treat-to-target goal in contrast to CR on and off Tx. Even more, LLDAS can be reached with limited use of corticosteroids with early introduction of immunosuppressives.

INTRODUCTION

Childhood-onset SLE (cSLE) has a more aggressive disease course than adult-onset SLE, characterised by a higher frequency and severity of organ involvement and damage accrual.1,2 Timely achievement of disease remission is important as ongoing disease activity is associated with lower health-related quality of life (HRQOL), development of damage and increased mortality. Treat-to-target has shown to be an effective strategy in various diseases and consists of strictly adjusting treatment until a specific predefined target is achieved.3 This target is most often disease remission, but can also be the lowest possible disease activity when remission is unobtainable.

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What is already known about this subject?

- Low Lupus Disease Activity State (LLDAS) in adult-onset SLE is associated with less flares and damage accrual. To date, no data are published on the achievability and applicability of LLDAS in the clinical management of children with lupus.

What does this study add?

- This is the first study which shows that LLDAS can be reached in all children with SLE. LLDAS is reached in a median of 6 months with limited use of corticosteroids and the majority of patients remain in LLDAS >50% of time.

How might this impact on clinical practice or future developments?

- Targeting LLDAS while using a strict corticosteroid-sparing regimen is a feasible treat-to-target strategy in the clinical management of childhood-onset SLE and will likely decrease damage accrual and improve health-related quality of life in children with SLE.

Recently, definitions of remission for SLE and recommendations for a treat-to-target strategy were described.3-5 Complete remission without receiving treatment was a stringent goal and was only achieved in less than 3% of patients with adult-onset SLE.6 Low Lupus Disease Activity State (LLDAS) allows (low) levels of disease activity in patients who are on stable treatment and low-dose prednisone, and was an achievable target in adult-onset SLE.3,4 Moreover, reaching LLDAS was associated with less damage accrual, reduced flare frequency, corticosteroid sparing and improved HRQOL.7 Currently, studies investigating LLDAS as a treat-to-target strategy in cohorts of children with SLE are lacking. This study investigated whether clinical remission (CR) and LLDAS are attainable goals in a well-defined longitudinal cSLE cohort.

METHODS

Patient characteristics

Patients fulfilled the revised American College of Rheumatology classification criteria or
the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, were diagnosed with SLE before 18 years of age and followed for at least 6 months (180 days) at the Erasmus Medical Center. All patients were diagnosed in our hospital and included at diagnosis in our prospective cohort study. Demographics, clinical characteristics and history of medication were prospectively collected from the date of diagnosis and during each follow-up visit using an electronic Case Record File (eCRF). Disease activity was assessed by Safety of Estrogen in Lupus Erythematosus National Assessment-SLE disease Activity Index (SELENA-SLEDAI), British Isles Lupus Assessment Group (BILAG-2004) and Physician Global Assessment (PGA) at each visit. Damage was measured at the last visit using the SLICC Damage Index (SDI).8

**Definition of CR and LLDAS**

Based on the Definitions of Remission in SLE (DORIS) framework, for each visit ‘CR off treatment’ (CR off Tx) was defined as a PGA ≤ 0.5, SELENA-SLEDAI=0, without prednisone or usage of other immunosuppressives. ‘CR on treatment’ (CR on Tx) was defined similarly, but allowed prednisone ≤ 5 mg/day and maintenance treatment with other immunosuppressives.4 LLDAS was defined as a SELENA-SLEDAI ≤ 4 with zero scores for renal, Central Nervous System (CNS), serositis, vasculitis and constitutional components, without an increase in any SLEDAI component since the previous visit, with a PGA ≤ 1 and prednisone dosage ≤ 7.5 mg/day. Immunosuppressives were allowed for LLDAS. Hydroxychloroquine treatment was allowed for all three definitions of disease remission.

**Statistics**

See online supplemental methods.

**RESULTS**

**Patient characteristics**

Fifty-one patients with cSLE were included within a total of 700 visits. The median follow-up per patient was 3.0 (0.5–12.0) years with median number of visits of 12 (4–43). Median disease activity at diagnosis was 8.0 (1–29) for the SELENA-SLEDAI, 2.0 (0.5–3.0) for the PGA and 10 (3–42) for the BILAG-2004. The most common involved organ systems at diagnosis according to the BILAG-2004 were the mucocutaneous domain (47.1%), followed by constitutional (41.2%) and renal domain (27.5%), respectively. The median number of organ systems involved at diagnosis was 3.1–6 The median SDI score at the last visit was 0 (0–1) (online supplemental table 1).

**Medication usage from diagnosis to last follow-up**

In our cohort and together with hydroxychloroquine usage (100%), prednisone (72.5%) and mycophenolate mofetil (MMF) (62.7%) were the most prescribed drugs. Within 3 months after diagnosis, 94.1% of the cSLE cases were on hydroxychloroquine and 60.8% used prednisone. Prednisone dosage decreased over time from a median of 0.74 (0.05–1.68) mg/kg/day at diagnosis to 0.44 (0.05–1.46) mg/kg/day at 3 months and 0.16 (0.05–1.54) mg/kg/day at 6 months after diagnosis. This decrease was paralleled by an increased usage of MMF (25.5% at diagnosis, 47.1% 3 months and 56.9% 6 months after diagnosis) (figure 1). Additional information is provided in online supplemental table 2.

**Disease remission**

LLDAS was achieved in all patients within a median time of 186 (28–846) days. Patients remained in this state for 693 (78–2676) days. Moreover, we assessed the cumulative time spent in LLDAS, since many studies have reported a 50% reduction in damage accrual in patients who have remained in LLDAS for 50% of their follow-up time.9 10 The majority (72.5%) of patients were in LLDAS for >50% of the follow-up time. At follow-up visits of patients not in LLDAS, the haematological, mucocutaneous and renal domains were most often still active according to the BILAG and SELENA-SLEDAI. CR on Tx was ever achieved in 52.9% of the patients within a median time of 415 (40–1585) days. These patients spent only 176 (35–1198) days of the total follow-up time in this state. Only four patients were able to stay in this state for >50% of the follow-up time. CR off Tx was achieved in 21.6% of patients within a median time of 536 (51–2103) days. These patients spent 176 (98–945) days of the total follow-up time in this state. Only one patient remained in this state for >50% of the follow-up time (table 1).

**Factors related to reaching LLDAS**

Patients who achieved LLDAS within 6 months had lower SELENA-SLEDAI and lower PGA scores at diagnosis than those patients who did not achieve LLDAS (online supplemental figure 1). Univariate analysis showed that SELENA-SLEDAI at diagnosis, PGA at diagnosis and prednisone dose at 3 months were associated with reaching LLDAS within 6 months. In the multivariate model, prednisone dose and MMF usage at 3 months were both associated with reaching LLDAS within 6 months. Here, a higher dose of prednisone at 3 months was associated with not reaching LLDAS within 6 months, while the use...
of MMF at 3 months was associated with reaching LLDAS within 6 months (table 2).

**DISCUSSION**

Previous work has shown that the majority of adults with cSLE do not achieve medication-free remission, develop significant damage at young age and have impaired HRQOL. Failure to achieve LLDAS within 6 months after diagnosis was associated with early damage accrual. In this study, we show that LLDAS is an achievable goal in cSLE with a

### Table 1  LLDAS and clinical remission

<table>
<thead>
<tr>
<th>Status ever achieved</th>
<th>LLDAS</th>
<th>CR on Tx</th>
<th>CR off Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status ever achieved</td>
<td>51 (100%)</td>
<td>27 (52.9%)</td>
<td>11 (21.6%)</td>
</tr>
<tr>
<td>Time to status in days, median (range)</td>
<td>186 (28–846)</td>
<td>415 (40–1585)</td>
<td>536 (51–2103)</td>
</tr>
<tr>
<td>Time in status in days, median (range)</td>
<td>693 (78–2676)</td>
<td>176 (35–1198)</td>
<td>176 (98–945)</td>
</tr>
<tr>
<td>% of time in status during follow-up, median (range)</td>
<td>72.1 (11.6–98.5)</td>
<td>17.9 (5–73.6)</td>
<td>17.4 (4.1–88.6)</td>
</tr>
<tr>
<td>Number (%) of patient in status &gt;50% of follow-up time</td>
<td>37 (72.5)</td>
<td>4 (14.8)</td>
<td>1 (9.1)</td>
</tr>
</tbody>
</table>

### Table 2  Binary logistic regression analysis of variables associated with achieving LLDAS at 6 months as outcome measure

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>P value</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>−0.014</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.074</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.047</td>
</tr>
<tr>
<td>SLEDAI at Dx</td>
<td>−0.14</td>
</tr>
<tr>
<td>BILAG at Dx</td>
<td>−0.016</td>
</tr>
<tr>
<td>PGA at Dx</td>
<td>−0.787</td>
</tr>
<tr>
<td>Number of domains involved</td>
<td>−0.323</td>
</tr>
<tr>
<td>SDI score at last visit</td>
<td>−1.099</td>
</tr>
<tr>
<td>HCQ use at 3 months</td>
<td>−0.777</td>
</tr>
<tr>
<td>Prednisone dose at 3 months</td>
<td>−2.729</td>
</tr>
<tr>
<td>MMF use at 3 months</td>
<td>0.56</td>
</tr>
</tbody>
</table>

A cut-off of p<0.100 was set to select the variables for the multivariate logistic regression.

**Table 1** LLDAS and clinical remission

**Table 2** Binary logistic regression analysis of variables associated with achieving LLDAS at 6 months as outcome measure

chosen treatment strategy, which included limited use of prednisone. Furthermore, patients with cSLE remained in LLRAS for the majority of their follow-up time. The follow-up in our study is too short to make reliable conclusions regarding the relation between LLRAS and damage accrual.

Evidence-based guidelines on initiation, tapering and cessation of corticosteroids do not exist for the management of SLE. Important differences in corticosteroid usage for cSLE treatment exist between medical centres, which are not associated with disease activity. Clinicians are reluctant to taper corticosteroids as this increases the chance of a lupus flare. In our centre, we have a strict corticosteroid-sparing treatment strategy to limit the well-known detrimental side effects of corticosteroids on damage accrual, including growth failure and HRQOL in children with SLE. In general, prednisone without other immunosuppressives is allowed for 3 months, after which other immunosuppressives are added to allow corticosteroid tapering. Here we show that within 6 months after diagnosis, prednisone dosages can safely be reduced in the majority of patients with cSLE when paralleled by increased use of immunosuppressives. Regression analysis revealed that a higher prednisone dose at 3 months was associated with not reaching LLRAS within 6 months, while MMF use at 3 months was associated with the opposite. This highlights the effectiveness of this strategy, which is consistent with the international consensus that indicates that immunosuppressives should be considered when prednisone dosages remain above 0.15 mg/kg/day.

Patients less prone to reach LLRAS within 6 months in general had a higher SELENA-SLEDAI and PGA scores at diagnosis, but the BILAG score was not discriminative. This is most likely explained by the fundamental differences between the scoring systems. The BILAG scores all organ domains equally, which is in contrast to the SELENA-SLEDAI. For example, renal activity, an organ system known for needing considerable time to become inactive, has a relative large contribution to the total SELENA-SLEDAI score.

This study has limitations. The size of our cohort is relatively small and therefore our results need to be validated in additional studies using larger cohorts of patients with cSLE. However, the detailed clinical data available from every patient since diagnosis, collected prospectively at each follow-up visit and the uniform treatment approach are strengths of this study and support the robustness of the conclusions drawn.

In conclusion, LLRAS is an achievable treat-to-target goal in cSLE and can be reached with limited use of corticosteroids with early introduction of immunosuppressives.

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Contributors Conceptualisation—MJW, MAV and SK. Acquisition of data—MJW, LvdB, DT, Kvr, Avd, SB, MV and SK. Data analysis—MJW, LvdB, MAV and SK. Interpretation—MJW, LvdB, MAV and SK. Drafting of the manuscript—MJW, LvdB, MAV and SK. All authors revised the manuscript critically and approved the final version.

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Competing interests None declared.

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