Collaboration set itself the task in 2013 of developing and validating a measure of low disease activity (LDA) for SLE, on the basis that remission as defined at that time was rarely attained, with the aspiration that a less stringent goal might still be associated with improved outcomes despite higher attainability. The use of careful consensus methodology yielded the Lupus Low Disease Activity State (LLDAS), which has now been shown in multiple independent cohorts to be attainable, but also highly protective from flare, damage accrual, low quality of life, and mortality. Validation studies include a multicentre prospective study, which confirmed that most definitions of remission were much less attainable but no more protective.

Attainability is important, and the combination of strong protection and good attainability has seen LLDAS deployed in many clinical trials, both post hoc and a priori, where it has discriminated active treatment from placebo in at least five trials.

Learning Objectives

- Discuss why, while remission is the goal of care for systemic lupus erythematosus, low disease activity may be more attainable and more pragmatic
- Describe how LLDAS is a thoroughly validated treat-to-target endpoint for SLE
- Explain why, compared with remission, the greater attainability of LLDAS enhances its performance as a clinical trial endpoint

LLDAS IS AN EXCELLENT OUTCOME MEASURE, BUT DOES IT REALLY CAPTURE PATIENTS WITH TRUE LDA?

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10.1136/lupus-2022-la.6

A precise definition of low disease activity (LDA) in systemic lupus erythematosus (SLE) is crucial for managing patients according to a T2T strategy. Lupus low disease activity state (LLDAS) was proven to be a valid outcome measure, since its achievement is associated with a significant decrease in disease flares and damage accrual, as well as with improved HR-QoL. Some pitfalls, however, may affect the definition of LLDAS:

1. LLDAS is not aligned with the DORIS definition of remission, particularly in the most important item - SLEDAI. Indeed, SLEDAI≤4 (including serology) is considered in the definition of LLDAS, but contrast clinical SLEDAI=0 is included in the DORIS definition. We know that a significant proportion of patients with SLEDAI≤4 have a clinical SLEDAI=0, since they are patients with serologically active clinical quiescent disease (SACQ). As a consequence, there is a great overlap between LLDAS and DORIS remission, i.e. the majority of patients in LLDAS are also in remission on therapy, according to the DORIS definition of remission. Thus, LLDAS cannot discriminate between patients in LDA and those in remission.

2. The item that could theoretically distinguish between remission and LLDAS is physician global assessment (PGA), which has a cut-off of ≤0.5 for remission and ≤1.0 for LLDAS. It is, however, very difficult to predict the phenotype of patients with a PGA in between 0.5 and 1.0, and a poor inter-rater and intra-rater reliability of PGA has been recently confirmed in a meta-analysis, which highlighted the need for PGA standardisation. Notably, in a recent paper testing different definitions of remission, PGA did not increase the performance of clinical SLEDAI=0 in predicting damage progression.

3. Thus, the remaining item able to distinguish patients in remission from those in LLDAS is glucocorticoid intake: ≤0.5 mg in remission according to the DORIS definition and ≤7.5 mg in LLDAS. It has, however, been shown that the great majority of patients in LLDAS receive a dosage of prednisone ≤5 mg/day; moreover, the habit of prescribing prednisone largely varies among rheumatologists, and cannot be easily standardised.

In addition, the major reason why LLDAS cannot capture patients in ‘true’ LDA is that it is based on the SLEDAI score, i.e. a binomial disease activity index that measures disease activity in each organ domain in terms of ‘present’ or ‘absent’, but it is not able to discriminate the level of disease activity within any single organ group.

A new disease activity index named SLE-DAS (http://sle-das.eu) has recently been proposed and validated, which measures disease activity in a continuous fashion and, thus, is more sensitive to clinical changes compared with the SLEDAI. The SLE-DAS includes some items that are not considered in the SLEDAI, namely lupus enteritis, cardiac and pulmonary manifestations and haemolytic anaemia. In addition, some items that are binomial in the SLEDAI were turned into continuous in the SLE-DAS, including arthritis, proteinuria, thrombocytopenia, and leucopenia. The SLE-DAS cut-offs for defining remission and LDA have recently been derived and validated.

Learning Objectives

- Discuss the hurdles in defining low disease activity in SLE and the pitfalls of LLDAS
- Discuss why LLDAS does not capture patients with ‘true’ LDA
- Explain lupus LDA in clinical practice, and discuss other instruments that might identify patients in LDA better than LLDAS

REFERENCES

Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral immunity with clear hints that abnormalities of B lineage cells (B and plasma cells) are key drivers.

Clinical experiences with belimumab as a first approved targeted SLE treatment provide robust evidence that blocking BLyS/BAFF selectively interfering with B cell survival can change the course of the disease, including prevention of damage accrual. Recent failures of first generation anti-CD20 (rituximab, ocrelizumab) and BTK inhibitors (fenemutibin/GDC-0853 and evobrutinib) together with the occurrence of anergic B cells in SLE provide the rational for various innovative strategies. These include more profound targeting by second generation anti-CD20 modalities (obinutuzumab) CD19 (CART, bispecific antibodies) or employing other immune targets, such as CD38 (daratumumab), or BAFFR (tanalumab).

In addition, enhancing regulatory B-cell functions may hold attractive opportunities. Such strategies have potential to reinstall the balance of pathogenic and protective B cells with the potential of more specific therapies. Moreover, these treatment targets should have the potential to overcome the status of anergic B cells holding promise to escape the detrimental chronic autoimmune process. In this context, targeting checkpoint molecules that downmodulate intracellular phosphatases, such as CD40 or other targets of this family on B cells, and enhancing Treg cells, may provide increased control of B-cell activation. Another potential innovative treatment modality could be the use of non-depleting bispecific antibodies may open more selective B cell subset targeting of enhancing the potency of depletion in the future.1–5

REFERENCES


