Bracalenti *et al. Rare Dis Orphan Drugs J.* 2025;4:28
DOI: 10.20517/rdodj.2025.10

Rare Disease and Orphan Drugs Journal

Review

Open Access

Remission and low disease activity in systemic lupus erythematosus

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How to cite this article: Bracalenti M, Iaccarino L, Doria A. Remission and low disease activity in systemic lupus erythematosus. *Rare Dis Orphan Drugs J.* 2025;4:28. https://dx.doi.org/10.20517/rdodj.2025.10

Received: 11 Feb 2025 **First Decision:** 3 Jul 2025 **Revised:** 20 Aug 2025 **Accepted:** 18 Sep 2025 **Published:** 10 Oct 2025

Academic Editor: Daniel Scherman **Copy Editor:** Ping Zhang **Production Editor:** Ping Zhang

Abstract

The treat-to-target strategy has significantly improved patient outcomes in several non-rheumatological disorders, such as diabetes mellitus, hypercholesterolemia, and arterial hypertension. This approach has also been successfully applied to certain rheumatological conditions, including rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies, and it has been proposed for systemic lupus erythematosus (SLE). However, identifying treatment targets in SLE remains challenging. The 2023 European Alliance of Associations for Rheumatology (EULAR) recommendations for SLE management emphasize remission or low disease activity (LDA) as the ideal treatment goals. Within this framework, the Definitions of Remission in SLE (DORIS) and Lupus Low Disease Activity State (LLDAS) are used to define remission and LDA, respectively, and also serve as secondary endpoints in an increasing number of randomized controlled trials. Achieving DORIS or LLDAS is associated with reduced mortality and improved health-related quality of life. Furthermore, reaching remission or LDA correlates with favorable patient outcomes, including fewer disease flares and lower damage accrual. Nevertheless, ongoing debates persist regarding the definitions of these states. This review aims to provide valuable insights into the main target disease activity states, highlighting their respective strengths and limitations in the context of clinical practice and future research.

Keywords: Remission, low disease activity, systemic lupus erythematosus, DORIS, LLDAS

INTRODUCTION

Despite significant advances in understanding the pathophysiology of systemic lupus erythematosus (SLE) and the development of novel therapies, patients with SLE continue to experience progressive organ damage, reduced health-related quality of life (HRQoL), and markedly increased mortality[1]. The treat-to-target (T2T) strategy has demonstrated substantial efficacy in chronic conditions such as arterial hypertension, hypercholesterolemia, and type 2 diabetes mellitus, even when using similar therapeutic approaches[2]. However, implementing T2T in SLE poses unique challenges due to the disease's heterogeneous clinical manifestations, the multitude of activity indices, and the absence of a single reliable biomarker for disease monitoring[3,4]. Consequently, defining remission or, alternatively, low disease activity (LDA) remains a complex and demanding task.

This unmet need has led to the development of multiple definitions of remission and, when remission is not feasible, of LDA, with the Definitions of Remission in SLE (DORIS) and Lupus Low Disease Activity State (LLDAS) being widely accepted by the international community, respectively[5,6].

This review aims to clarify the concepts of remission and LDA, examining their various definitions to guide clinical decision-making and their use as outcome measures in randomized controlled trials (RCTs). It will also discuss future directions for implementing these definitions within the T2T strategy for SLE management.

METHODS

This work focuses on the various definitions of remission and LDA and their associations with damage accrual, disease flares, and mortality.

The literature search was conducted in PubMed, Embase, and Scopus using a set of predefined keywords combined with SLE.

We considered all the papers published between June 2014 and December 2024. Keyword strategies were discussed and agreed upon collectively to ensure consistency throughout the manuscript and included key terms as "remission", "DORIS", "low disease activity", "LLDAS", "quality of life", "HRQoL", "patient reported outcomes", "disease activity", "damage", "Systemic Lupus International Collaborating Clinics - Damage index (SLICC-DI)", "mortality", "disease flares", "treat to target".

Additionally, the snowballing technique was allowed, in order to identify other relevant studies.

We prioritized high-quality evidence, including RCTs, prospective cohort studies, large case-control studies, and meta-analyses. Grey literature, such as expert consensus statements and conference abstracts, was excluded from this study.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the study selection process is reported in Figure 1.

Figure 1 outlines the number of records identified, screened, assessed for eligibility, and included in the final synthesis, along with reasons for exclusion at each stage.

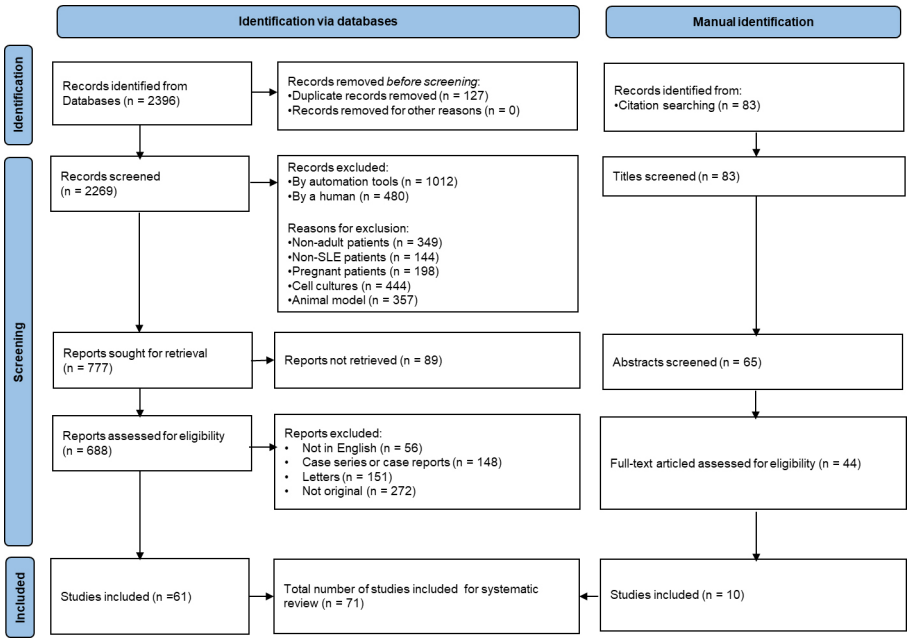

Figure 1. PRISMA Flow Diagram illustrating the study selection process for the literature review. PRISMA: Preferred reporting items for systematic reviews and meta-analyses; SLE: systemic lupus erythematosus.

REMISSION

The T2T paradigm has been proposed for patients with SLE; however, no consensus exists on the definition of remission, resulting in multiple interpretations over the past decade [Table 1].

This prompted the formation of a task force of 60 SLE experts in 2014 to agree on a potential definition of remission in SLE[14]. They defined remission as a desirable outcome for SLE patients, characterized by a durable state with at least the absence of major symptoms and signs of SLE. This collective effort culminated in 2021 with the proposal of a final DORIS definition[5].

The DORIS definition of remission includes a Clinical Systemic Lupus Erythematosus Disease Activity Index (cSLEDAI) of 0, a Physician Global Assessment (PGA) < 0.5, and a glucocorticoid ceiling of 5 mg/day prednisone equivalent. Permitted treatments include antimalarial agents and stable maintenance doses of immunosuppressive or biologic agents (see Table 2).

The inclusion of the PGA is intended to compensate for the known limitations of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2k). As a matter of fact, the SLEDAI-2k score has been demonstrated in some studies to be only a modest predictor of organ damage accrual[15,16]. Moreover, the dichotomous nature of the SLEDAI-2k impairs its sensitivity to partial changes in disease activity[17], unlike semiquantitative indices such as systemic lupus erythematosus disease activity state (SLEDAS)[18,19]. For example, Jesus *et al.* showed that a change of ≥ 4 points in the SLEDAI-2k score between visits failed to detect almost two-thirds of clinically relevant changes in disease activity as judged by the physician[20]. The addition of PGA also aids in assessing some manifestations not included in the SLEDAI-2k score, such as hemolytic anemia, gastrointestinal disease, myelitis, and pneumonitis[21]. Nonetheless, as shown in Table 1, DORIS is the only definition of remission featuring the inclusion of the PGA which has been debated due to its low inter-rater and intra-rater reliability in a systematic review[22], prompting international efforts to reach a standardization consensus [Physician Global Assessment International Standardization COnsensus

Table 1. Definitions and attainability of SLE remission according to the studies published in the last 10 years

Definition of remission	Disease activity	Therapy allowed	Attainability
Zen *et al.*, 2015 - (Padua remission)[7]-	SLEDAI-2k = 0	AMA only	7.1% of patients, at least 5 years long
complete remission	cSLEDAI-2k = 0	AMA, PDN 0 mg, table IS, bDMARDs	14.7% of patients, at least 5 years long
-Clinical remission off steroids	cSLEDAI-2k = 0	AMA, PDN ≤ 5 mg/day, stable IS, bDMARDs	15.6% of patients, at least 5 years long
-Clinical remission on steroids			
Ugarte-Gil *et al.*, 2017[8]	SLEDAI = 0	AMA, PDN ≤ 5 mg/day, stable IS	20.5% of patients, at least once
Polachek *et al.*, 2017[9]	cSLEDAI-2k = 0	AMA	30.8% of patients, at least one year long
Tselios *et al.*, 2019[10]	cSLEDAI-2k = 0	Unlimited	10.1% of patients, at least 10 year long
Alarcón *et al.*, 2019[11]	SLAM = 0	AMA, PDN ≤ 5 mg/day	1.8% of all visits
Jesus *et al.*, 2021[12]	SLEDAS ≤ 2.08	AMA, PDN ≤ 5 mg/day, stable IS, bDMARDs	Not investigated, (100% concordance with DORIS)
van Vollenhoven *et al.*, 2021 - (DORIS)[5]	cSLEDAI-2k=0, PGA< 0.5	AMA, PDN ≤ 5 mg/day, stable IS, bDMARDs	67.9% of patients, no specific duration
Ugarte-Gil *et al.*, 2022[13]	cSLEDAI-2k = 0	AMA, PDN ≤ 5 mg/day, stable IS	40.7% of patients, no specific duration

Each definition is accompanied by disease activity criteria, allowed treatment regimen and reported attainability data. DORIS: Definitions of remission in SLE; cSLEDAI-2k: clinical systemic lupus erythematosus disease activity index 2000; PDN: prednisone; AMA: antimalarial agents; stable IS: stable immunosuppressive agents; bDMARDs: biologic disease-modifying antirheumatic drugs; SLEDAI: systemic lupus erythematosus disease activity index; SLAM: systemic lupus activity measure; SLEDAS: systemic lupus erythematosus disease activity state, PGA: physician global assessment; SLE: systemic lupus erythematosus.

Table 2. The 2021 DORIS definition of SLE

Clinical SLEDAI = 0
Physician global assessment < 0.5
Antimalarials, prednisone ≤ 5 mg/day and/or stable immunosuppressants, including biological DMARDs are allowed
Serology not included

SLEDAI: Systemic lupus erythematosus disease activity index; SLE: systemic lupus erythematosus; DORIS: definitions of remission in SLE; DMARDs: disease-modifying antirheumatic drugs.

in Systemic Lupus Erythematosus (PISCOS)][23]. Therein, it was stated that only experienced physicians should be rating the PGA, preferably the same rater at each visit, making its use particularly challenging in multicenter and longitudinal studies. Moreover, another review by Ugarte *et al.* has shown that remission, regardless of definition, was protective against damage accrual, even in the absence of the PGA, suggesting that its addition may not add significant value[24].

Despite this, the PGA remains a part of the DORIS definition due to its independent association with adverse outcomes in some studies[22].

The DORIS definition deliberately excludes serological activity as no unequivocal linear correlation has been found between serological markers (complement and anti-dsDNA levels) and disease activity in SLE. In fact, recent literature suggests that abnormal serology may be only modestly associated with increased risk of future flares, especially renal flares[25] and it does not consistently correlate with organ damage in patients who are otherwise clinically inactive[26]. Moreover, requiring serological normalization would render remission unattainable for many, thereby reducing its applicability in both clinical trials and routine care. This exclusion also reflects the significant heterogeneity in laboratory techniques, with a lack of technical standardization across assays that compromises the reliability and reproducibility of serological measurements. Additionally, the interpretation of serological activity may benefit from a more nuanced, semiquantitative framework: subtle deviations from normal levels may carry limited clinical significance,

whereas more pronounced abnormalities are more likely to correlate with adverse outcomes, including disease relapse.

Although the DORIS task force acknowledged the importance of duration in defining remission, it refrained from specifying precise time windows, fearing that additional restrictions would reduce attainability. Robust evidence from RCTs, with the post-hoc analysis of the TULIP-1 trial serving as a prominent example, reported a DORIS attainment rate of merely 15.3% at one year of treatment with anifrolumab[27] which increased up to 30.3% after 4 years[28]. The following real-world studies[11,29-39], while limited by their observational design and absence of controlled conditions, reveal considerable variability in attainability, which is strongly influenced by the duration of follow-up [Table 1].

For instance, in the longitudinal Hopkins Lupus Cohort, patients spent 27% and 13% of their follow-up time in DORIS remission on-treatment and off-treatment, respectively[29]. In a multinational longitudinal cohort study of the Asia Pacific region, patients were in DORIS remission for 36.1% of the time while on treatment and 10.8% of the time while off treatment[30].

However, durability is a key aspect of remission. A growing body of evidence has shown that prolonged remission may significantly influence patient outcomes, describing a positive association between the cumulative time spent in remission and mitigation of damage accrual[11,31,32]. More specifically, spending longer than five years in remission in the Amsterdam cohort[31] and longer than two years in the Padova cohort[33,34] was associated with protection against damage accumulation (see Table 3). Interestingly, a recent paper from Golder *et al.*[35] illustrated that remission intervals as short as 3 months may already yield tangible benefits in terms of damage accrual [hazard ratio (HR) 0.66; 95% confidence interval (95%CI) 0.57-0.76; $P < 0.0001$], with longer durations correlating with incrementally deeper levels of protection (HR 0.48; 95%CI 0.38-0.60; $P < 0.0001$ - for 36 months)[36-38].

Remarkably, not only the time intervals but also the proportion of follow-up spent in remission is seemingly tied to positive clinical outcomes: attaining DORIS remission for < 25% of the observed follow-up was associated with approximately a 50% reduction in organ damage by SLICC-DI (see Table 3)[29]. Moreover, being in DORIS for longer than 50% of the time was able to predict about a 40% reduction in damage accrual and a 60% reduction in severe flares with high specificity (85.2% and 95.1%, respectively)[39]. A comparison of the effects of various remission criteria and their duration on long-term outcomes is reported in Table 3. It is important to note that wide variation in follow-up duration limits comparability across the studies reported hereafter, as short observation periods may underestimate time-dependent outcomes such as relapse and organ damage, which often emerge in the long term.

Glucocorticoid-free remission

In SLE, the pursuit of glucocorticoid-free remission reflects a broader shift toward minimizing long-term treatment toxicity while preserving disease control. Although sustained remission off-treatment remains relatively uncommon, emerging evidence suggests that this goal may be more attainable than previously assumed in the pre-biologic era.

The feasibility of glucocorticoid-free remission varies widely across patient populations depending on baseline disease activity and treatment status. In an active SLE cohort described by Oiwa *et al.* (2024)[40], only 28.3% of patients were able to discontinue glucocorticoids over five years whereas withdrawal rates reached 84.6% among patients already in clinical or complete remission on low-dose prednisone (≤ 5 mg/day) over six years, as reported by Tani *et al.* (2019)[41].

Table 3. Impact of various remission definitions on damage accrual and relapse rate

Outcome	Study	Design	N. patients	Definition and duration of remission	Mean FU	RE pooled estimates	*P*
Damage accrual ^	Zen *et al.*, 2015[7]	Retrospective	224	Padua, ≥ 5 years	5.0 years	RR 0.40 (0.20-0.78)	0.008
	Tsang-A-Sjoe *et al.*, 2017[31]	Retrospective	183	Padua, ≥ 5 years	5.0 (3.1-5.3) years	OR 0.20 (0.07-0.53)	0.001
	Ugarte-Gil *et al.*, 2017[8]	Prospective	1,480	SLEDAI = 0 off-therapy*	2.4 (0.7-5.6) years	HR 0.51 (0.35-0.75)	0.0006
	Petri *et al.*, 2018[29]	Prospective	1,356	DORIS, < 25% of FU	46 (1-292) person-months	RR 0.54 (0.44-0.67)	< 0.0001
	Golder *et al.*, 2019[30]	Prospective	1,707	DORIS, ≥ 50% of FU	2.19 (1.51-2.99) years	HR 0.49 (0.38-0.65)	< 0.0001
	Saccon *et al.*, 2020[34]	Retrospective	646	DORIS, ≥ 2 years	5.0 years	OR 0.48 (0.33-0.70)	< 0.0001
	Golder *et al.*, 2024[35]	Prospective	3,449	DORIS, > 3 months	2.8 (1.1-5.6) years	HR 0.66 (0.57-0.76)	< 0.0001
	Pitsigavdaki *et al.*, 2024[39]	Retrospective	348	DORIS, ≥ 6 months	54 ± 18 months	HR 0.58 (0.36-0.93)	< 0.05
Relapse rate ^^	Golder *et al.*, 2019[30]	Prospective	1,707	DORIS, ≥ 50% of FU	2.19 (1.51-2.99) years	HR 0.54 (0.46-0.63)	< 0.0001
	Golder *et al.*, 2024[35]	Prospective	3,449	DORIS, > 3 months	2.8 (1.1-5.6) years	HR 0.60 (0.51-0.71)	< 0.0001
	Pitsigavdaki *et al.*, 2024[39]	Retrospective	348	DORIS, ≥ 6 months	54 ± 18 months	HR 0.14 (0.08-0.27)	< 0.001

For each study, the corresponding reference, study design, number of enrolled patients, remission definition with time criteria, mean follow-up duration, and pooled estimates from the random effects model with *P*-values are reported. ^ by SLICC-DI; ^^ by SELENA flare index * For this specific reference, the estimate is based on the cumulative number of visits in remission, with only AMA permitted during this state. DORIS: Definitions of remission in SLE; FU: follow-up period; N: number of patients enrolled; AMA: antimalarial agents; SLEDAI: systemic lupus erythematosus disease activity index; SLICC-DI: systemic lupus international collaborating clinics damage index; SELENA flare index: safety of estrogens in lupus erythematosus national assessment flare index; RE pooled estimates: random effects model pooled estimates; *P*: *P*-value; HR: hazard ratio; OR: odds ratio; RR: risk ratio; SLE: systemic lupus erythematosus; each RE pooled estimate is reported with its 95% confidence interval (95%CI).

As expected, the duration of follow-up appears to be a critical factor as well. Long-term data from the belimumab trial extension[42] showed a 15% increase in glucocorticoid withdrawal over seven years, indicating that glucocorticoid tapering and discontinuation often require considerable time.

Recent real-world data underscore the survival advantage of achieving remission without glucocorticoids. Patients who maintained DORIS-defined remission for ≥ 50% of the observed time had a HR for mortality of 0.52 (0.29-0.93), while those in glucocorticoid-free DORIS remission for the same duration exhibited an even more profound reduction in mortality risk (HR 0.13; 95%CI 0.02-0.96)[43].

Moreover, long-term (≥ 5 years) remission on glucocorticoids has been associated with increased damage accrual compared to glucocorticoid-free remission in real-life data[33]. This difference appeared insignificant in the shorter term (1-4 years of remission), possibly suggesting that organ damage is driven primarily by disease activity in the short term and by treatment toxicity in the long term. Conversely, other studies suggest no relevant differences in overall protection from damage accrual between sustained glucocorticoid-free remission and remission on low-dose glucocorticoids[35], though glucocorticoid-free remission was significantly associated with lower relapse rates. However, in a monocentric Italian cohort[44], patients in remission who discontinued glucocorticoids did not experience significantly higher flare rates compared with those who maintained them ($P = 0.81$).

Thus, the notion that remission on-treatment and off-treatment yield equivalent outcomes remains highly controversial, as glucocorticoid withdrawal may confer additional long-term benefits in both disease control and treatment toxicity. Nevertheless, the DORIS definition remains intentionally more lenient regarding permitted therapies compared to other remission definitions, out of concern that stricter criteria could encourage overly aggressive withdrawal of necessary treatments with potentially harmful consequences. Cautious tapering therefore remains essential.

LOW DISEASE ACTIVITY

When remission cannot be achieved, LDA may serve as a pragmatic treatment goal. Although LDA represents an intermediate state between remission and high disease activity, its exact boundaries are difficult to define. As a result, multiple definitions of LDA have been proposed over the years [Table 4].

Among the various definitions of LDA, the Asia Pacific Lupus Collaboration (APLC) criteria-namely, the LLDAS-are the most widely applied in clinical studies of SLE[6]. Established in 2016, LLDAS allows a SLEDAI score of ≤ 4, provided it does not reflect major organ involvement, new features compared with the previous assessment, hemolytic anemia, or gastrointestinal activity. It also requires a PGA ≤ 1 and a prednisone (or equivalent) dose ≤ 7.5 mg/day. Conceptually, LLDAS was defined as a state which, if sustained, carries a low risk of adverse outcomes by balancing disease activity with medication safety. Although distinct from remission, this definition overlaps substantially with it. Indeed, Golder *et al.*[30,47] stated that up to 75% of visits classified as LLDAS were also in remission by the DORIS definition, while only 25% represented LLDAS without remission.

Understandably, such a consistent overlap has opened the avenue for speculation around the actual benefits conferred by attainment of LDA without remission, given the vast array of studies merging the two. Similarly, considering the often relapsing-remitting course of SLE, it has also been postulated that LDA could represent only a transient state of passage, a sort of dividing line, between disease activity and remission rather than an independent entity[21]. Such interpretations imply that most, if not any, improvement of patient outcomes tied to achievement of LDA may, thus, be spurious and only driven by its proximity to remission.

Nonetheless, a growing body of evidence indicates that LDA and remission may instead represent a spectrum of disease states, a clinical gradient associated with increasingly favorable patient prognoses[35]. Hence, continuous measures of disease activity such as SLEDAS which establish a clear cut-off between remission and LDA, may be more appropriate to capture the subtle nuances of disease activity without the ambiguity generated by potential overlaps[12,46].

Emerging evidence highlighted that LDA can be sustained for prolonged periods on end and yield tangible benefits independently of an overlap with remission. It was recently illustrated that even excluding remission, a short time spent in LLDAS (< 25% of the follow-up) was still associated with a substantial reduction in organ damage rates [adjusted rate ratio (aRR) 0.75 - 95%CI 0.61-0.91][48]. Longer durations in LDA (> 75% of follow-up) were proportional to organ damage reduction (aRR 0.35 - 95%CI 0.28-0.44) especially in the musculoskeletal, renal, and cardiovascular domain[48].

Additionally, it has been suggested that the time threshold necessary for LLDAS to yield any protective effect on damage accrual may be as low as 3 months (HR 0.60; 95%CI 0.51-0.71; $P < 0.0001$)[30]. A dose-effect of deepening protection was described with progressively longer durations of sustained LLDAS in a previous work as well[35]. This dose-dependent beneficial effect also seems to extend to the improvement of

Table 4. Definitions and attainability of SLE LDA according to the studies published in the last 10 years

Definition of LDA	Disease activity	Therapy allowed	Attainability
Franklyn *et al.*, 2016 - (LLDAS)[6]	SLEDAI-2k ≤ 4, PGA ≤ 1.0	AMA, PDN ≤ 7.5 mg/d, stable IS, bDMARDs	88.5% of patients, at least once (including remission)
Ugarte-Gil *et al.*, 2017[8]	SLEDAI ≤ 4	AMA, PDN ≤ 7.5 mg/d, stable IS	34.4% of patients, at least once (14.2% excluding remission)
Polachek *et al.*, 2017 - (LDA-TC)[9]	cSLEDAI-2k < 3	AMA	43.7% of patients, at least one year long (12.9% excluding remission)
Tselios *et al.*, 2019[10]	cSLEDAI-2k ≤ 2	Unlimited	28.1% of patients, at least 10 years long (18.0% excluding remission)
Alarcón *et al.*, 2019[11]	SLAM ≤ 3	AMA, PDN ≤ 7.5 mg/d	16.9% of all visits, (15.1% excluding remission)
Tani *et al.*, 2018 - (LLDAS5)[45]	SLEDAI-2k ≤ 4, PGA ≤ 1.0	AMA, PDN ≤ 5 mg/d, stable IS, bDMARDs	73.9% of patients through the follow-up (26.1% excluding remission)
Assunção *et al.*, 2022[46]	SLEDAS ≤ 2.48	AMA, PDN ≤ 7.5 mg/d, stable IS, bDMARDs	Not reported (~100% agreement with LLDAS)
Ugarte-Gil *et al.*, 2022 - (mLLDAS)[13]	SLEDAI-2k ≤ 4	AMA, PDN ≤ 7.5 mg/d, stable IS	50.8% of all visits (5.6% excluding remission and LDA-TC)

Each definition is accompanied by disease activity criteria, allowed treatment regimen and reported attainability data. LDA: Low disease activity; LLDAS: lupus low disease activity state; cSLEDAI-2k: clinical systemic lupus erythematosus disease activity index 2000; PDN: prednisone; AMA: antimalarial agents; stable IS: stable immunosuppressive agents; bDMARDs: biologic disease-modifying antirheumatic drugs; SLEDAI: systemic lupus erythematosus disease activity index; SLAM: systemic lupus activity measure; cSLEDAS: clinical systemic lupus erythematosus disease activity state; PGA: physician global assessment; SLE: systemic lupus erythematosus; LDA-TC: LDA definition - Toronto Clinic; mLLDAS: modified LLDAS.

HRQoL and flare rates[38,39]. In fact, attainment of LLDAS for ≥ 60% of time or ≥ 36 months was found to be the time proportion threshold exhibiting the highest specificity (88.1%) for correlation with reduced severe flares [incident rate ratio (IRR) 0.71; 95%CI 0.57-0.88; $P = 0.001$], hospitalization (IRR 0.70; 95%CI 0.53-0.91; $P = 0.007$), and mortality rates (IRR 0.13; 95%CI 0.03-0.65; $P = 0.013$)[39]. An associated reduced mortality rate had already been described with the achievement of LLDAS ≥ 50% of the time (HR 0.31; 95%CI 0.16-0.62; $P < 0.01$)[49]. Multiple cohort studies have established the comparability between LDA, especially if sustained, and remission in terms of organ damage accrual (mLLDAS IRR 0.76; 95%CI 0.65-0.89; remission-on-treatment IRR 0.68; 95%CI 0.62-0.75)[13], mortality (LLDAS50 HR 0.51; 95%CI 0.31-0.85; $P = 0.010$; *vs.* DORIS50 HR 0.52; 95%CI 0.29-0.83 $P = 0.027$)[43] and flare rates (complete remission and LDA for ≥ 10 years: $P = 0.23$)[10]. In fact, attaining LLDAS for ≥ 60% of time or ≥ 3 years was associated with damage-free progression, akin to attaining DORIS ≥ 2 years or ≥ 50% of follow-up[39].

Nonetheless, it should be underscored that not only the duration but also the timing of its attainment is critically important. Indeed, the inability to attain LLDAS within 6 months from diagnosis was associated with early damage accumulation in a predominantly Caucasian cohort (see Table 5)[50]. A shorter disease duration from diagnosis was found to correlate with the probability and rapidity of achievement of LLDAS, i.e., ≤ 12 months (HR 1.37; 95%CI 1.16-1.61; $P < 0.001$)[51]. Further evidence suggests that early attainment of LLDAS (≤ 12 months from diagnosis) may be tied to an increase in the probability of attaining a prolonged LDA (LLDAS ≥ 50%) and demonstrates a potential advantage in glucocorticoid intake as well[52]. Unfortunately, only 7.6% and 51.9% of patients achieved LLDAS at 6 and 12 months in this same cohort, respectively.

Table 5 summarizes the main clinical outcomes associated with different definitions of LDA of varying durations. Herein, meaningful differences in follow-up duration across studies hinder comparability, particularly in assessing the temporal evolution of organ damage and relapses.

Table 5. Impact of various LDA definitions on damage accrual and relapse rate

Outcome	Study	Design	N. patients	Definition and duration of LDA	Mean FU	RE pooled estimates	*P*
Damage accrual ^	Ugarte-Gil *et al.*, 2017[8]	Prospective	1,480	SLEDAI ≤ 4, off-glucocorticoids*	2.4 (0.7-5.6) years	HR 0.62 (0.43-0.87)	0.007
	Piga *et al.*, 2017[50]	Retrospective	107	LLDAS, ≤ 6 months from diagnosis	18.0 months	OR 0.20 (0.06-0.67)	0.009
	Tsang-A-Sjoe *et al.* 2017[31]	Retrospective	183	LLDAS ≥ 50% of FU	5.0 (3.1-5.3) years	OR 0.52 (0.28-0.99)	0.046
	Petri *et al.*, 2018[29]	Prospective	1,356	LLDAS, 25%-49% of FU	46 (1-292) person-months	RR 0.63 (0.48-0.84)	0.0012
	Golder *et al.*, 2019[30]	Prospective	1,707	LLDAS ≥ 50% of FU	2.19 (1.51-2.99) years	HR 0.54 (0.42-0.70)	< 0.0001
	Alarcón *et al.*, 2019[11]	Prospective	558	SLAM ≤ 3, PDN ≤ 7.5 mg/d	6 (4-6) visits	RR 0.18 (0.12-0.26)	< 0.0001
	Golder *et al.*, 2024[35]	Prospective	3,449	LLDAS > 3 months	2.8 (1.1-5.6) years	HR 0.60 (0.51-0.71)	< 0.0001
	Pitsigavdaki *et al.*, 2024[39]	Retrospective	348	LLDAS ≥ 6 months	54 ± 18 months	HR 0.61 (0.43-0.86)	< 0.01
Relapse rate ^^	Golder *et al.*, 2019[30]	Prospective	1,707	LLDAS ≥ 50% of FU	2.19 (1.51-2.99) years	HR 0.41 (0.35-0.48)	< 0.0001
	Golder *et al.*, 2024[35]	Prospective	1,356	LLDAS, 25%-49% of FU	2.8 (1.1-5.6) years	HR 0.56 (0.51-0.63)	< 0.0001
	Pitsigavdaki *et al.*, 2024[39]	Retrospective	1,707	LLDAS ≥ 50% of FU	54 ± 18 months	HR 0.19 (0.13-0.27)	< 0.001

For each study, the corresponding reference, study design, LDA definition with time criteria, number of enrolled patients, mean follow-up duration, and pooled estimates from the random effects model with *P*-values are reported. ^ by SLICC-DI; ^^ by SELENA flare index. * For this specific reference, the estimate is based on the cumulative number of visits in remission, with only AMA permitted during this state. LDA: Low disease activity; LLDAS: lupus low disease activity state; FU: follow-up; N: number of patients enrolled; PDN: prednisone; AMA: antimalarial agents; SLEDAI: systemic lupus erythematosus disease activity index; SLAM: systemic lupus activity measure; SLICC-DI: systemic lupus international collaborating clinics damage index; SELENA flare index: safety of estrogens in lupus erythematosus national assessment flare index; RE pooled estimates: random effects model pooled estimates; *P*: *P*-value; HR: hazard ratio; OR: odds ratio; RR: risk ratio; SLE: systemic lupus erythematosus; each RE pooled estimate is reported with its 95% confidence interval (95%CI).

Interestingly, ethnic differences also appear to influence the time required to achieve LDA[53]: Multiethnic cohorts have shown that African American patients may take nearly twice as long as Caucasian patients to reach comparable rates of LLDAS (Caucasians: 52% at one year, 76% at two years; African Americans: 36% at one year, 58% at two years)[54]. This finding is consistent with previous reports of higher disease activity and greater organ damage among African American patients, even after adjustment for socioeconomic factors[29].

Potential predictors of LDA were identified as the lack of articular, mucocutaneous, renal and hematological involvement[39,44,55], use of immunosuppressive drugs, lower disease activity early in the disease course[56] and older age[57].

Intriguingly, meaningful differences exist within the LDA spectrum itself as the absence of serological activity may identify a subset of LDA patients with better patient outcomes than their serologically active counterparts, in line with a recent study reporting that LLDAS with neither clinical nor serological activity bears the strongest protective association with severe flares (clinically and serologically quiescence: HR 0.21; 95%CI 0.14-0.33; $P < 0.001$ *vs.* serological activity: HR 0.33; 95%CI 0.26-0.42; $P < 0.001$)[58].

However, it is important to emphasize that most of the evidence supporting the association between LDA and favorable outcomes comes from observational cohort studies[10,13,29,35,38,39,43,48-52]. While these studies provide valuable insights, they are inherently limited by potential confounding and the inability to establish causality. In contrast, fewer but more methodologically rigorous data are available from RCTs[59], notably BLISS-52 and BLISS-76, in which SLEDAS LDA successfully discriminated between treatment and placebo arms (OR 1.53; 95%CI 1.07-2.20; $P = 0.019$)[60].

TREAT TO TARGET STRATEGY IN SLE

The T2T strategy involves adjusting treatments at predetermined intervals to achieve specific, clinically relevant goals. This approach has been successfully applied to chronic conditions such as diabetes, hypertension, and hyperlipidemia, using evidence-based targets such as glycated hemoglobin, blood pressure, and cholesterol levels. Large RCTs have shown that T2T yields superior outcomes compared to standard care, even without new therapeutic agents[61].

In rheumatology, T2T is more complex due to the need to normalize multiple parameters simultaneously, often represented in a composite score. This complexity can lead to misclassification of treatment responses, especially in chronic conditions with irreversible damage. The T2T concept was first explored in rheumatoid arthritis through the Tight Control in Rheumatoid Arthritis (RA) (TICORA) trial, which revealed that T2T resulted in better treatment responses, higher remission rates, and less radiographic damage compared to standard of care[62]. Subsequent studies confirmed T2T efficacy in RA, exhibiting improvements in physical function and HRQoL. T2T is now firmly embedded in The European Alliance of Associations for Rheumatology (EULAR) treatment recommendations for RA. The benefits of T2T have also been demonstrated in other rheumatological diseases, such as psoriatic arthritis and gout[63-64].

Although an international task force formulated recommendations for implementing T2T in SLE (DORIS) in 2014, more than a decade after its initial theoretical proposal, an RCT formally comparing this approach with standard of care in SLE remains unpublished. This delay may suggest that while a rigid framework is suitable for RCTs, it may be inadequate for a complex and heterogeneous disease such as SLE. More flexible and personalized strategies, rather than a "one size fits all" approach, may be required to achieve remission or LDA in routine clinical practice[65,66].

The T2T approach should be regarded as a stepwise process: the initial target is the induction of remission or, alternatively, LDA; the second target is the maintenance of these states; and ultimately, the tapering or withdrawal of glucocorticoids and immunosuppressive therapies[3]. Unfortunately, relapses are common in SLE, particularly after discontinuation of glucocorticoids or immunosuppressants, making it extremely challenging to balance damage related to disease activity with that related to treatment. Notably, most studies investigating relapse risk during treatment tapering or withdrawal have not included patients receiving biologic disease-modifying antirheumatic drugs (bDMARDs)[67,68].

In line with the paradigm shift promoted by the latest EULAR treatment recommendations, biologics may aid in decreasing disease activity and facilitate the delicate transition to treatment withdrawal and de-escalation while ensuring satisfactory safety profiles[69].

FUTURE DIRECTIONS

Although DORIS and LLDAS have been extensively validated in numerous real-world studies, the search for improved definitions of remission and LDA should continue. Reliance on the SLEDAI-2k score and the PGA carries intrinsic limitations in assessing disease activity, highlighting the need for more sensitive,

continuous, and inter-rater reliability indices. Additionally, because certain types of disease activity are more strongly associated with damage accrual, new target state definitions should consider using appropriately weighted scoring for these manifestations.

Furthermore, the lack of alignment among these definitions, which often leads to overlaps between DORIS remission and LLDAS, represents a critical issue to be addressed in future research. Developing an enhanced and unified definition of remission and LDA is essential for their use as secondary endpoints in RCTs. At the same time, multiple definitions tailored to account for heterogeneity in ethnicity, demographics, and access to care may be required to better suit different patient cohorts in routine clinical practice. Similarly, the influence of ancestry, socioeconomic status, healthcare system, and access to care on achieving LLDAS (or remission) remains underexplored, despite these disparities being recognized as significant contributors to poor outcomes in SLE[70,71]. The impact of early diagnosis and timely therapy initiation is another relevant aspect that warrants further investigation.

Moreover, because most current data come from observational real-world studies, causality between attainment of these target states and improved patient outcomes cannot yet be inferred. Therefore, head-to-head interventional trials comparing standard-of-care regimens with the T2T approach, specifically targeting DORIS remission and LLDAS, are urgently needed.

Despite a strong theoretical basis and expert advocacy for T2T in SLE, the appropriate medication adjustments when targets are not met remain unclear.

Additionally, implementing the T2T approach necessitates more frequent patient evaluations, yet there is no consensus on the optimal interval between clinical assessments. This could potentially pose logistical challenges in real-world practice though novel digital technologies may assist in this regard. Moreover, this approach could prompt frequent therapy changes, affecting adherence and healthcare costs. Setting less stringent targets such as LDA at early stages may be beneficial to avoid abrupt and overly zealous therapeutic changes, considering the limited therapeutic armamentarium available.

As relapses are common in SLE, T2T targets should include a minimum duration in DORIS remission or LLDAS to ensure positive outcomes. Further research is needed to establish a consensus on the minimum protective duration. However, time proportion thresholds appear to be valuable surrogate measures for assessing positive outcomes without the need for longer waiting periods, making them particularly useful in the context of RCTs.

Moreover, further studies are needed to elucidate the role of serology in predicting flares and to determine whether it should be included in the definitions of remission or LDA.

Novel biologic therapies for SLE patients can help achieve the ambitious goals of DORIS remission and LLDAS, potentially reducing disease progression, improving HRQoL, lowering mortality, and reducing healthcare costs.

CONCLUSIONS

Remission and LDA represent contiguous yet clinically distinct target disease states, for which multiple definitions have been proposed over the years, with DORIS remission and LLDAS being the most widely accepted. Achieving these states is associated with significant reductions in adverse patient outcomes-such as damage accrual, disease flares, and mortality-while also improving HRQoL. However, both DORIS

remission and LLDAS have intrinsic limitations, highlighting the need for better definitions. A unified definition, free from equivocal overlap between the two, could serve as a more reliable and discriminative endpoint in clinical trials. Personalized definitions tailored to individual patients may be more appropriate for routine clinical practice. Further research, alongside the development of new biological therapies, could enable the successful and widespread implementation of the T2T strategy in everyday care.

DECLARATIONS

Acknowledgement

The graphical abstract was created using BioRender and Microsoft Office, both accessed under institutional licenses provided by the University of Padova. (Created in BioRender. Bracalenti M (2025) https://BioRender.com/hqpnfie).

Authors' contributions

Made substantial contributions to the conception and revision of the review: Doria A, Iaccarino L
Made substantial contributions to the drafting of the review: Bracalenti M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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