

“TREAT-TO-TARGET” IN SYSTEMIC LUPUS ERYTHEMATOSUS: NOVEL DEFINITIONS OF REMISSION AND LOW DISEASE ACTIVITY

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Abstract. *Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with alternating periods of activity and remission, where an accurate assessment of disease activity remains crucial for optimal treatment. For this purpose, various instruments and composite measures have been developed to enable objective evaluation and effective patient monitoring. In recent years, the SLE Disease Activity Score (SLE-DAS), validated in 2019, has emerged as a reliable and precise method. It combines 17 clinical and laboratory parameters, offering a more accurate assessment of disease activity. Furthermore, SLE-DAS defines clear criteria for remission and low disease activity, supporting the “treat-to-target” approach. Despite the significance of SLE-DAS, other scales such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and its modified versions, Systemic Lupus Activity Measure (SLAM), SLAQ (Systemic Lupus Activity Questionnaire), and the British Isles Lupus Assessment Group (BILAG) Index continue to be used in clinical practice. Of these, SLEDAI-2K remains the most frequently employed tool in daily rheumatological practice. Despite the variety of tools available, SLE-DAS stands out for its precision, practicality, and wide applicability, both in routine clinical practice and clinical trials, emphasizing its broad utility in managing SLE.*

Key words: *systemic lupus erythematosus, disease activity; treat-to-target*

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by alternating episodes of activity and remission. Despite significant advancements in understanding the pathophysiology of SLE and the development of new therapeutic approaches, patients with SLE remain at risk for progressive organ damage, impaired health-related quality of life (HRQoL), and substantially increased mortality. The complex immunopathogenesis and heterogeneity of clinical manifestations make the assessment and monitoring of lupus patients challenging [1, 2]. This requires the implementation of composite measures to objectively assess disease activity. Accurate disease activity assessment is key for optimal treatment and long-term monitoring of patients with SLE. Over the years, numerous tools have been developed to assess disease activity, focusing primarily on clinical manifestations and laboratory parameters, with some including patient self-assessment. In clinical practice, tools such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and its modified versions, Systemic Lupus Activity Measure (SLAM), Systemic Lupus Activity Questionnaire (SLAQ), and the British Isles Lupus Assessment Group (BILAG) Index are used [3, 4]. The most commonly used tools remain BILAG and SLEDAI-2K (5). Despite their use-

fulness, these methods show limitations regarding sensitivity and applicability in different clinical contexts [6]. In recent years, the SLE Disease Activity Score (SLE-DAS) has established itself as a reliable and adaptive tool. Developed and validated in 2019, SLE-DAS combines 17 clinical and laboratory parameters, providing a more detailed and accurate assessment of disease activity [7]. One of the key features of SLE-DAS is the introduction of new definitions for low disease activity and remission, providing clear and standardized criteria for treatment goals [8]. The modern “treat-to-target” approach, which focuses treatment on achieving specific and measurable goals such as remission or low disease activity, is fundamental for effective disease management [9, 10]. Disease activity assessment in patients with SLE is also included in current recommendations from the European Alliance of Associations for Rheumatology (EULAR), which advises disease activity assessment at each patient visit [11]. Similarly, Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends five key domains to be evaluated in clinical trials for SLE, including disease activity [12]. In this context, SLE-DAS offers a reliable tool for monitoring therapeutic goals, with its definitions of low disease activity and remission

providing well-validated and widely applicable criteria for evaluating treatment success.

The aim of this review is to explore the existing tools for assessing disease activity in SLE, with a focus on the practical applicability of SLE-DAS for monitoring disease activity and treatment outcomes, and to present the "treat-to-target" strategy as an approach for optimal disease monitoring.

A literature review was conducted on the methodologies published in recent years for assessing disease activity in patients with systemic lupus erythematosus. A search was performed in the PubMed and Google Scholar databases using keywords: "treat-to-target", PGA, SLEDAI, SLEDAI-2K, SLEDAI-2KG, SLE-DAS, BILAG, SLAM, SLAQ, Definitions of Remission in SLE, Lupus Low Disease Activity State. Several thousand publications related to different methods of assessing activity in SLE were found. For example, "SLEDAI" and its modifications (SLEDAI-2K, SLEDAI-2KG) have been cited in over 4,000 articles. After applying full-text availability and English language criteria, about 10-15% of the articles were eliminated due to lack of full texts, and an additional 5-10% were removed due to language barriers. After these limitations were applied, between 1,500 and 2,000 relevant publications were identified and analyzed. The found literature sources were systematically organized and discussed in this review.

METHODS FOR ASSESSING DISEASE ACTIVITY

Physician Global Assessment (PGA) is a key element in monitoring disease activity. PGA is a 100-mm visual analog scale (VAS) proposed by Liang and colleagues in 1989 to quantitatively assess overall disease activity on a range from 0 to 3 [13]. This tool is sensitive to changes in patients' conditions but requires significant clinical experience for reliable and consistent application. One of the main drawbacks of PGA is the high variability in assessments. A recent systematic review of the scientific literature shows that the definition and application of PGA are heterogeneous, highlighting the need for further standardization [14]. Despite these limitations, PGA remains a widely used tool and a key component of the leading indices for assessing therapeutic response in systemic lupus erythematosus. PGA is included in the primary indices used as a primary endpoint in clinical trials, such as the SLE Responder Index (SRI) and the BILAG-based responder

index. Additionally, PGA plays an important role in defining key conditions such as low disease activity (LLDAS) and remission (DORIS), which are critical criteria for monitoring long-term disease control [15].

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was created in 1985 in Toronto, Canada, by a team including rheumatologists, nephrologists, and methodology experts with extensive experience in systemic lupus erythematosus (SLE). This index includes 24 clinical and laboratory criteria and has become the most widely used tool for assessing disease activity both in daily clinical practice and in clinical trials [16]. The initial version of SLEDAI was developed to evaluate the patient's condition over a 10-day period. The reliability of the index has been confirmed in various clinical settings, including routine practice and multiple studies. Data show that SLEDAI has prognostic value regarding mortality and the accumulation of damage in patients with SLE [17,18]. Due to these qualities, SLEDAI remains an important tool for assessing disease activity and progression, assisting in making informed clinical decisions.

Safety of Estrogens in Lupus Erythematosus National Assessment Trial (SELENA)-SLEDAI is a modified version of the original SLEDAI, with additions that expand the scope of disease assessment. The main difference is in the definition of visual disturbances, which in SELENA-SLEDAI also includes conditions such as scleritis and episcleritis. Additionally, this instrument integrates a definition for disease flare based on SLEDAI, taking into account changes in therapy as well as the Physician Global Assessment (PGA) [19].

SLEDAI-2000 (SLEDAI-2K) is an enhanced version for precise assessment of disease activity. SLEDAI-2K was created to overcome some limitations of the original SLEDAI in longitudinal monitoring of patients. The initial definitions in SLEDAI only account for disease activity based on newly emerged or worsened signs. However, this creates a risk of missing persistent symptoms, such as when proteinuria remains high but does not increase further between visits. In 2002, Gladman et al. modified the index so that any presence of an active sign is scored, regardless of whether it is newly emerged or persistent. This change allows for a more accurate assessment of current disease activity based on signs such as rash, alopecia, mucosal manifestations, and proteinuria. The validity of SLEDAI-2K has been confirmed through comparison with the original SLEDAI, with a

very high correlation coefficient between the two instruments 0.97. The main difference between them is the scoring of both newly appeared and recurring symptoms in SLEDAI-2K, which makes this index more reliable for long-term monitoring of patients with systemic lupus erythematosus [20].

SLEDAI-2K 30-day version is an adaptation for longer follow-up intervals. The original SLEDAI and its 2000 modification (SLEDAI-2K) assess disease activity signs that are present at the time of the examination or during the previous 10 days. However, in clinical practice and research, manifestations over a longer time frame up to 30 days are typically monitored (21). This led to the creation of the SLEDAI-2K 30-day version, which is more suitable for use in clinical trials and for long-term monitoring. Studies show similar results between the 10-day and 30-day versions of SLEDAI-2K, confirming the reliability of the new adaptation [22]. Disease manifestations in systemic lupus erythematosus typically persist for more than a month, making the 30-day version more practical for clinical use. However, SLEDAI-2K has shown limited sensitivity to changes in disease activity-between 14.9% and 47.4% for improvement and 26.2% and 59.1% for worsening [6].

SLEDAI-2K Glucocorticoid Index (SLEDAI-2KG) – Integration of Corticosteroid Dose: Another modification of SLEDAI-2K is the SLEDAI-2K Glucocorticoid Index (SLEDAI-2KG), which incorporates the daily corticosteroid dose into the overall assessment of disease activity. This version more accurately reflects the impact of therapy on the patients' condition [23]. This addition makes SLEDAI-2KG a useful tool for evaluating both disease activity and the therapeutic burden of corticosteroid treatment.

Systemic Lupus Activity Measure (SLAM) was developed in 1989 in Boston using disease manifestations described by the American Rheumatology Association Council on SLE. This tool includes a total of 30 indicators – 23 clinical and 7 laboratory, grouped into 11 categories covering various organs and systems. SLAM assesses overall disease activity over the past month, with a maximum possible score of 86 points. **SLAM-Revised (SLAM-R)** is an adaptation focused on clinical manifestations. The modified version, SLAM-Revised (SLAM-R), was developed to simplify the application of the original index by including only 23 clinical manifestations and providing results in a range from 0 to 81 points. The immunological indicators are excluded in SLAM-R, making the tool easier to use in routine practice. However, it includes a number of subjective symptoms, such as fatigue, shortness of breath, and

chest pain, which are not always a result of systemic lupus erythematosus (SLE) activity [24]. This adaptation strikes a balance between the detail of the assessment and practical applicability but requires caution when interpreting subjective complaints, which may be influenced by other underlying factors.

Systemic Lupus Activity Questionnaire (SLAQ) is a tool for assessing disease activity based on SLAM, developed in 2003. Its primary feature is that it excludes laboratory parameters, focusing instead on symptoms reported by patients themselves. SLAQ consists of 24 items reflecting symptoms associated with nine different organs and systems [25]. Patients evaluate their symptoms over the past three months in terms of severity, ranging from mild to moderate and severe. This enables the tool to provide a subjective yet meaningful assessment of disease activity from the patient's perspective. Studies have shown a moderately high correlation between SLAQ and SLAM scores, confirming the alignment between the two tools. Furthermore, additional research has demonstrated good reliability, validity, and sensitivity of SLAQ, making it a useful tool in clinical practice and scientific research [26]. SLAQ offers a valuable perspective on disease activity by incorporating patients' evaluations of their condition, complementing objective clinical data.

British Isles Lupus Assessment Group (BILAG). Index was developed in 1988 by a team of British and Irish rheumatologists as a tool for the comprehensive assessment of disease activity in SLE [27]. The revised BILAG-2004 is an enhanced tool that includes 97 items grouped into 9 domains, covering various organs and systems: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiopulmonary, gastrointestinal, ocular, renal, and hematological manifestations. Each of these items is evaluated based on observations from the previous 4 weeks using a scale: 0 – no activity; 1 – improvement; 2 – unchanged; 3 – worsening; 4 – new onset activity. Based on the results, disease activity is classified into five categories: A – severe disease activity, requiring high doses of oral corticosteroids (prednisolone > 20 mg/day) or systemic immunomodulators; B – moderate activity; C – mild activity; D – latent disease in previously affected organs or systems; E – no disease involvement. Compared to the original index, which contained 86 items, BILAG-2004 adds gastrointestinal and ocular manifestations, as well as category E [28]. Despite its high reliability and detail, BILAG-2004 is rarely used in routine clinical practice due to the complexity of its assessment. Instead, it is popular in clinical trials as part of the disease response assess-

ment indices such as the Systemic Lupus Responder Index (SRI) and the BILAG-based Composite Lupus Assessment (BICLA). To facilitate its use, a simplified version, Easy-BILAG, was recently developed by Carter et al. [29]. **Easy-BILAG** shows high accuracy in determining disease activity while offering a faster and easier assessment method. Due to these advantages, its use is recommended over BILAG-2004 whenever the tool is required in clinical practice.

SLE Disease Activity Score (SLE-DAS) is a relatively new tool for assessing disease activity in SLE, developed and validated by Jesus et al. in 2019. The study included 520 patients from specialized lupus centers in Portugal and Italy [7]. **Characteristics of SLE-DAS.** **SLE-DAS** uses 17 clinical and laboratory parameters, with conditions such as arthritis, proteinuria, leukopenia, and thrombocytopenia assessed using a scoring system. The remaining parameters are assessed dichotomously – presence or absence. Access to the tool is facilitated by an online SLE-DAS calculator: <https://SLEDAS.eu> (Figure 1). Compared to SLEDAI-2K, SLE-DAS provides lower scores for localized mucocutaneous manifestations compared to generalized skin rashes, less weight for mucocutaneous manifestations compared to sys-

temic vasculitis, inclusion of cardiopulmonary manifestations, and hemolytic anemia, making the tool more comprehensive. **Validity of SLE-DAS.** During validation, SLE-DAS demonstrated higher sensitivity and specificity for detecting clinically significant changes in disease activity and more accurately predicted the risk of damage compared to SLEDAI-2K [6, 7]. Recent studies confirm the reliability of the tool. In a cohort of 117 patients, SLE-DAS showed similarity with SLEDAI-2K in determining low disease activity through Lupus Low Disease Activity State (LLDAS) [30]. Two studies found similarities between the two tools in assessing HRQoL [31, 32]. SLE-DAS also demonstrated strong reliability as a predictor of SLE flare-ups during the second and third trimesters of pregnancy [33]. Furthermore, SLE-DAS showed a strong correlation with SLEDAI-2K ($r = 0.720$, 95% CI = 0.5727 to 0.8231, $R^2 = 0.5193$, $p < 0.001$) in a population of 61 Bulgarian patients with SLE [34] (Figure 2). In conclusion, SLE-DAS is a modern, reliable, and comprehensive tool for assessing disease activity in SLE, offering advantages both in clinical practice and scientific research.

“Treat-to-target” (T2T) strategy, applied in a variety of chronic diseases, focuses on achieving

Fig. 1. Online SLE-DAS calculator <https://SLEDAS.eu>

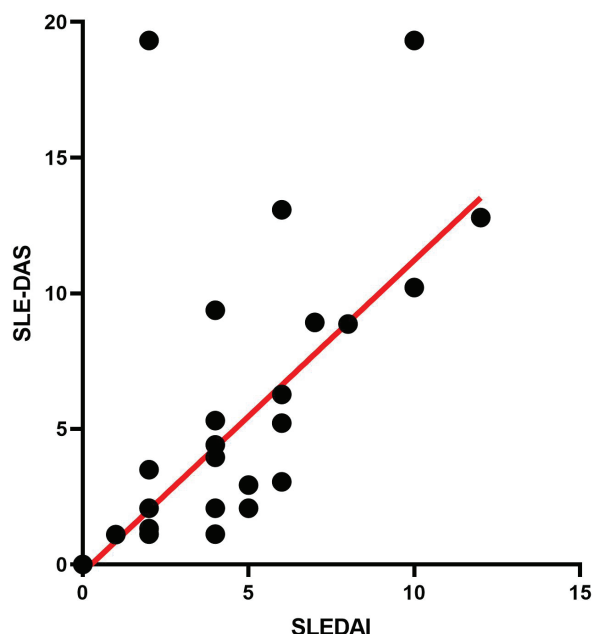


Fig. 2. Correlation between SLEDAI-2K and SLE-DAS (Pencheva D, Monov S)

clearly defined and clinically significant treatment goals, such as low disease activity and remission. This strategy involves regular adjustments to a patient's therapeutic regimen at specific intervals, with the aim of reaching the target state [9, 35]. In systemic lupus erythematosus (SLE), these goals typically include achieving low disease activity and even remission [36, 37]. With advancements in therapeutic options, such as newly adopted treatments, the „treat-to-target“ (T2T) concept has begun to be successfully integrated into clinical practice, leading to more effective disease management [38]. Remission and low disease activity are central to the „treat-to-target“ strategy. Although these two concepts are closely related, they represent different levels of control over disease activity and provide distinct treatment goals. Defining these states as endpoints in clinical trials allows for the evaluation of the effectiveness of various therapeutic strategies. It is important to note that there are several different definitions for remission and low disease activity, which are used in monitoring disease activity.

Definitions of Remission in SLE (DORIS). The initial conclusions of the working group developing the consensus for the definition of remission in SLE were published in 2016. The criteria for achieving remission are primarily based on clinical assessment and include:

- cSLEDAI = 0 (clinical assessment of disease activity)
- PGA < 0.5 (Physician's Global Assessment of global disease activity, with a scale from 0 to 3)

- Corticosteroid dose (prednisolone or equivalent) ≤ 5 mg/day

- Use of antimalarials and/or immunosuppressants and biologics

At this stage, the definition does not include the patient's perspective or the evaluation of quality of life [36].

LLDAS (Lupus Low Disease Activity State) is the most widely validated tool for assessing a state of low disease activity in lupus and represents a more achievable treatment goal compared to remission as defined by DORIS [37]. However, there are limitations in accurately determining the disease activity state, including the state of low disease activity. LLDAS is based on SLEDAI-2K, which does not include severe manifestations of SLE, such as hemolytic anemia, and cardiopulmonary, pulmonary, and gastrointestinal manifestations. To address these gaps, the LLDAS definition adds PGA (Physician's Global Assessment), including disease activity manifestations not covered by SLEDAI-2K, as well as information about current treatment and therapy changes.

The criteria for achieving LLDAS include:

- SLEDAI-2K ≤ 4 , with no activity in major organs and systems (kidneys, CNS, cardiovascular, pulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal manifestations
- No new disease activity compared to the previous assessment
- PGA ≤ 1 (Physician's Global Assessment of global activity)

➤ Corticosteroid dose ≤ 7.5 mg/day or well-tolerated standard immunosuppressive therapy and approved biologic agents.

Achieving LLDAS is associated with fewer disabilities, flare-ups, and improved quality of life, as measured by the physical and mental component summary of the SF-36 [39, 40]. LLDAS has been validated and is used as an endpoint in numerous studies. In a post-hoc analysis of the MUSE study with Anifrolumab, reaching LLDAS successfully distinguishes patients who respond to treatment from those who do not [41]. Indices like LLDAS and the definition of remission in SLE play an important role in the treatment of SLE, providing clear and measurable goals for assessing treatment effectiveness, enabling an objective evaluation of treatment progress within the “treat-to-target” (T2T) strategy.

Remission Based on SLE-DAS. LLDAS and DORIS are not the only definitions of low disease activity and remission in SLE. In 2021, the working group that developed the SLE-DAS disease activity assessment tool proposed a definition for remission based on SLE-DAS. Diogo Jesus and colleagues successfully validated this new definition, demonstrating its proven equivalence to the DORIS remission definition [8]. The criteria for achieving remission based on SLE-DAS are:

- SLE-DAS = 0, and
- Current prednisone dose (or equivalent) ≤ 5 mg/day

This definition offers a clearer and more precise assessment of patients' condition and has been validated in clinical practice, demonstrating its practical value and compatibility with other established criteria.

LDA (Low Disease Activity) Based on SLE-DAS: In 2022, Helena Assunção and colleagues

developed and validated a new definition for low disease activity (LDA) based on SLE-DAS. Validation demonstrated its good discriminatory ability to identify patients in a state of low disease activity [42]. The criteria for achieving SLE-DAS-based low disease activity (SLE-DAS LDA) are:

- SLE-DAS ≤ 2.48 , and
- Current prednisone dose (or equivalent) ≤ 7.5 mg/day.

Additionally, the SLE-DAS definition for LDA establishes thresholds for different categories of disease activity, which do not overlap:

- Mild activity: $2.08 < \text{SLE-DAS} \leq 7.64$
- Moderate/severe activity: $\text{SLE-DAS} > 7.64$.

The SLE-DAS definition for low disease activity has several key differences compared to other systems. First, it requires only the assessment of disease activity and corticosteroid dose, without the need for prior evaluation data or the Physician's Global Assessment (PGA). Second, the scoring system in SLE-DAS is more advanced than SLEDAI-2K, making the definition for low disease activity more precise and better differentiated (Table 1). This allows SLE-DAS to clearly distinguish between patients in true remission and those in a state of low disease activity [8]. These advantages make SLE-DAS-based LDA not only a valuable tool for routine clinical practice but also beneficial in the context of clinical trials. In a post-hoc analysis of a phase III clinical trial with belimumab, it was shown that SLE-DAS remission and SLE-DAS LDA effectively differentiated patients receiving active treatment from those on placebo, demonstrating the potential of this tool for clinical application [43].

In conclusion, systemic lupus erythematosus is a complex autoimmune disease that requires precise

Table 1. Comparison between LLDAS, SLE-DAS LDA, DORIS remission and SLE-DAS remission

Criteria	LLDAS	SLE-DAS LDA	DORIS Remission	SLE-DAS Remission
SLEDAI-2K	≤ 4	—	Clinical cSLEDAI = 0	SLE-DAS = 0
Activity of major organs and systems	No activity in kidneys, CNS, CVS, lungs, vasculitis, fever, and no hemolytic anemia or gastrointestinal manifestations	No new signs of disease activity compared to the previous assessment	No activity in major organs and systems	No new signs of disease activity compared to the previous assessment
SELENA-SLEDAI PGA	≤ 1 (scale 0–3)	—	PGA < 0.5 (0–3)	—
Current prednisone dose (or equivalent)	≤ 7.5 mg/day	≤ 7.5 mg/day	≤ 5 mg/day	≤ 5 mg/day
Treatment with immunosuppressive drugs	Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologics, excluding drugs in clinical trials	—	Use of antimalarials and/or immunosuppressors and/or biologics	Use of antimalarials and/or immunosuppressors and/or biologics

LLDAS: Lupus Low Disease Activity State; LDA: Low Disease Activity; DORIS: Definition of Remission in SLE; SLE-DAS: SLE Disease Activity Score

tools for assessing disease activity. The concepts of low disease activity and remission are key components of the “treat-to-target” strategy, and advanced methods such as SLE-DAS provide a more accurate assessment and support the achievement of this goal, significantly contributing to improved outcomes in both clinical practice and scientific research.

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