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Systemic lupus erythematosus: management strategies

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by multisystem involvement and various phenotypes. It follows a relapsing-remitting course, marked by alternating periods of relative inactivity and disease flares that can lead to organ damage, significant morbidity, and increased mortality. Approximately half of patients with SLE develop organ damage within 5 years of diagnosis. Potentially modifiable risk factors for damage include uncontrolled disease activity/severe flares, and glucocorticoid exposure. This review outlines a strategy to reduce disease activity and prevent organ damage, emphasizing early diagnosis, maintenance of low disease activity with minimal corticosteroid use, and flare prevention. Early recognition is crucial to avoid disease progression and prevent the development of more severe phenotypes. The 2019 EULAR classification criteria strike a balance between specificity and sensitivity but exclude ANA-negative patients, who may represent up to 20% of cases at diagnosis. To address this limitation, we introduced the SLE Risk Probability Index (SLERPI), a simple, clinician-friendly, machine learning-based model that does not require ANA positivity as a criterion; a score > 7 in SLERPI has shown 94.2% accuracy. Reducing the frequency and severity of flares is a major treatment goal to prevent organ damage and achieve remission or maintain low disease activity. The 2023 EULAR recommendations suggest the early use of biological agents to control disease activity, reduce flares, and facilitate corticosteroid dose reduction and damage prevention. However, incomplete response or refractory disease remains a significant challenge for both patients and clinicians, with evidence suggesting that response rates decline with each

subsequent flare. Globally, new approaches are being explored that target various cellular and molecular pathways, including B cells, T cells, and CAR-T cells. The use of CAR-T cell technology to profoundly deplete B cells has shown promising results.

Keywords: Systemic lupus erythematosus, disease activity, organ damage, flares, therapy discontinuation

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by multisystem involvement and a wide spectrum of phenotypes, ranging from asymptomatic cases to life-threatening manifestations[1]. The disease typically follows a relapsing-remitting course, with alternating periods of low disease activity or remission. Approximately 20%-30% of SLE patients experience chronically active or persistently quiescent disease[2]. Severe and/or refractory SLE can lead to irreversible organ damage and is associated with increased mortality rates[3,4].

Early diagnosis of SLE enables prompt therapeutic intervention and may prevent organ damage. In this context, new diagnostic tools are crucial for the early detection of SLE, particularly to address the diagnostic gap in antinuclear antibody (ANA)-negative patients, who account for approximately 20% of cases. The SLE Risk Probability Index (SLERPI) is a simple, clinician-friendly, machine learning-based model designed to assist in differentiating SLE from other rheumatic diseases. A SLERPI score > 7 has been shown to achieve 94.2% accuracy. The model includes 14 classical features, weighted variably, including hematologic, neurologic, and immunologic disorders, serositis, synovitis, and rash[5].

Despite the introduction of new disease-modifying conventional and biologic agents, most patients continue to experience recurrent disease exacerbations[1]. A multicenter observational inception cohort study conducted across nine Latin American countries, using a case-crossover design and a shared database, showed that each flare doubles the risk of organ damage, regardless of severity[6]. According to the European Alliance of Associations for Rheumatology (EULAR) recommendations for SLE management, preventing disease flares is a primary treatment goal. Additional key targets include improving long-term survival, minimizing organ damage, reducing treatment-related toxicities, and optimizing health-related quality of life[7,8]. Effective management of SLE requires a comprehensive approach that addresses multiple aspects of the disease, including reducing disease activity, preventing flares and organ damage, and mitigating adverse events of therapy. Moreover, considerations such as comorbidities, fertility, survival, and quality of life are essential pillars of SLE management and are discussed in detail below[1].

Disease activity

Measuring lupus disease activity remains a challenging and complex task for both clinicians and researchers[9]. The multi-systemic nature and variability of lupus complicate the accurate evaluation of disease activity. Numerous attempts have been made to quantify lupus activity[9,10]. However, the lack of a standardized instrument with sufficient reliability, validity, and sensitivity remains an unmet need[10]. Notwithstanding these limitations, assessing disease activity is fundamental to the current management of SLE[10].

Three primary tools are widely used to evaluate lupus activity: the British Isles Lupus Assessment Group index (BILAG-2004), the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and the Physician Global Assessment (PGA). The BILAG-2004 index is an organ-based, transitional activity tool with good negative prognostic value. It provides disease activity scores over the past 4 weeks across eight

organ systems using an ordinal scale from A to E, based on the physician's intention to treat. The index categorizes disease activity into five levels (A to E), which correspond to modifications in current treatment and help differentiate lupus activity and severity[1,9-11].

The SLEDAI-2K is another widely used instrument that evaluates overall lupus activity by summing scores from 24 descriptors across nine organ systems present in the last 30 days. It evaluates both new-onset and persistent activity and includes serological parameters in its scoring. However, it has notable limitations, such as the inability to grade severity, partial response, or worsening within individual organs or systems[1,9,10].

The PGA is a subjective, standardized score used internationally to assess lupus activity based on the clinician's overall judgment of all manifestations. It is rated on a visual analogue scale from 0 to 3, where 0 indicates no activity, 0.5-1 mild activity, and > 2-3 severe activity. Due to its subjective nature, the PGA is generally used alongside other objective measures[10].

In addition to these global indices, organ-specific outcome measures are employed to assess lupus nephritis (LN) and cutaneous lupus erythematosus[9]. Complete clinical renal response is defined as proteinuria less than 0.5-0.7 g/24 h by 12 months, while a reduction of at least 50% in proteinuria by 6 months constitutes a partial clinical response[12]. Improvement in proteinuria combined with normalization or stabilization of glomerular filtration rate (GFR) should be ideally achieved within the first three months of treatment[12]. The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a validated tool for measuring both activity and damage in cutaneous lupus erythematosus, describing disease extent based on the intensity of involvement across different anatomical areas[9].

In our clinical practice, we primarily use the SLEDAI-2K due to its simplicity and speed, in combination with the PGA. Disease activity is recommended to be assessed at every visit, while serological activity and routine laboratory tests should be monitored every three to six months, depending on the current disease status, risk factors for flare, frequency and severity of prior flares, and ongoing treatment.

Damage index

Irreversible organ damage is a major outcome in SLE and is associated with high morbidity and mortality rates[4]. High disease activity, major organ involvement, comorbidities, and the use of immunosuppressive agents - especially corticosteroids - are all linked to increased organ damage. The Systemic Lupus International Collaborating Clinics Damage Index (SDI) is a useful tool that assesses damage across 12 organ systems in patients with SLE, regardless of its cause. Damage may result from persistent disease activity, recurrent flares, adverse events of treatment, or intercurrent illnesses such as infections, surgery, or cancer. The SDI enables both the quantification of organ damage and differentiation from active disease, and it helps guide adjustments to immunosuppressive therapy to prevent further complications such as toxicity, infections, and hospitalizations. The SDI should be evaluated every 6 months or annually; in most clinical practices, including ours, it is assessed yearly. Each item should be scored if it has been present for at least 6 months[1,13,14].

Lupus exacerbations (flares)

Lupus flares, which can be classified as mild, moderate, or severe, contribute substantially to organ damage[6]. Therefore, preventing flares and achieving low disease activity or remission are crucial goals for patients with SLE. In general, a flare is defined as a measurable increase in disease activity in one or more organ systems, characterized by new or worsening clinical signs and symptoms and/or laboratory

abnormalities[11,15-18]. Evaluating clinical and laboratory activity at every visit, along with identifying risk factors for flares, plays an important role in both prevention and early detection. However, there is no universally accepted and validated tool for the quantification of lupus flares.

The two most commonly used instruments for assessing SLE flares are the SELENA-SLEDAI Flare Index (SFI) and the BILAG 2004 Flare Index[6,14,17,19].

SELENA-SLEDAI flare index (SFI): This index combines clinical and laboratory changes captured by the SLEDAI with the physician's global assessment [17,19,20]. A ≥ 3-point increase in the SELENA-SLEDAI score indicates a flare, reflecting clinically significant deterioration; an increase to a total score > 12 defines a severe flare[15,20]. The SFI also highlights the need for hospitalization due to a lupus flare[1].

BILAG 2004 flare index: The BILAG 2004 index evaluates new or worsening clinical signs and symptoms in each organ system over time under specific treatments[19-21]. Changes in disease activity within each organ domain are scored as severe (one A score), moderate (≥ 2 B scores), or mild (one B score or ≥ 3 C scores) flares[20,21]. The severity of a flare guides adjustments in GC doses, including intravenous pulses or prednisone ≥ 20 mg/day (as in BILAG A scores), as well as the use of immunosuppressants[20,21]. BILAG 2004 captures the physician's intention to treat and guides treatment modifications aimed at achieving low disease activity and/or remission.

In our practice, we use a combination of the SFI and the current PGA to evaluate lupus flares and guide therapeutic decisions, owing to their simplicity.

Health-related quality of life

Health-related quality of life (HRQoL) encompasses the functional, social, and emotional aspects of a patient's life. Disease activity in SLE can significantly affect HRQoL, impacting physical, social, and psychological well-being[1,22]. The goal of disease modification is to improve or normalize quality of life, physical functioning, and social and work capacity[23]. Patient-reported outcomes (PROs) are used to evaluate the effect of interventions on aspects that are meaningful to patients[24]. Several validated SLE-specific instruments, including LupusPRO and Lupus QoL, have demonstrated utility in clinical practice. LupusPRO is a 43-item SLE-specific questionnaire that assesses QoL longitudinally, covering both HRQoL and non-HRQoL domains such as goals and desires, coping strategies, social support, and satisfaction with care[22,25]. LupusQoL is a 34-item questionnaire designed to assess eight domains: physical health, emotional health, fatigue, pain, planning, body image, intimate relationships, and perceived burden to others. It is typically administered every four weeks[1,22,25].

Among the most widely used standardized generic tools to measure HRQoL in SLE patients are the 36-item Short Form Health Survey (SF-36) and the EuroQoL five-dimensional questionnaire (EQ-5D). The SF-36 is particularly useful for comparing the health status of patients with that of the general population. The EQ-5D is a simple questionnaire that integrates clinical and economic data[22,25].

Prevention of severe disease and flares

SLE patients who experience disease exacerbations are at increased risk of developing irreversible damage and end-stage organ dysfunction[6]. Preventing lupus flares by identifying patients at high risk is crucial for reducing organ damage[6,16]. Ethnicity, male sex, age at disease onset, and a history of severe organ involvement are important predictors of lupus exacerbations[16,26]. Specifically, African-American ethnicity (odds ratio [OR] 1.8 compared to Caucasian ethnicity), male sex, and disease onset at or before age 25

(hazard ratio [HR] 2.1) are significant risk factors for flares. Major organ involvement, such as nephritis (HR 4.8), neuropsychiatric manifestations (HR 2.5-3.1), cytopenias, and persistent disease activity, are also strong predictors of flares[15,16]. Serological activity, indicated by elevated anti-double-stranded DNA antibodies and/or low complement levels - particularly low C3 - is associated with an increased risk of exacerbations[20]. Therefore, frequent evaluation of these immunological markers every 3 to 6 months is recommended in clinical practice, especially for high-risk patients. Similarly, urinalysis should be performed at every visit or at least every 3 to 6 months, especially in patients with LN.

Hydroxychloroquine (HCQ) plays an important role in preventing lupus flares. Several observational and controlled studies have shown that reducing or discontinuing HCQ increases the risk of SLE flares (OR 2.5), including renal flares, compared to patients who continue therapy[27,28]. Early use of biologic agents also appears to reduce the severity and/or frequency of flares. In the BLISS clinical trials, prevention of severe flares was a key secondary endpoint[26,29-31]. Stohl *et al.* demonstrated that patients receiving belimumab were 49% less likely to experience a severe flare compared with those receiving placebo over 52 weeks (HR 0.51 [95%CI: 0.35-0.74]; $P = 0.0004$)[31]. Consequently, EULAR strongly recommends the early inclusion of biologics, such as belimumab, in the therapeutic protocol for SLE[7].

TREAT-TO-TARGET STRATEGIES IN SLE

Achieving disease remission or low disease activity is the main treatment goal for lupus experts, as these states are associated with numerous favorable outcomes[32]. According to the DORIS Task Force, remission in SLE is defined by a clinical SLEDAI score of 0, a PGA score < 0.5, a prednisolone dose ≤ 5 mg/day, and a stable dose of antimalarials and immunosuppressive agents[9]. Lupus low disease activity state (LLDAS) is defined by an SLEDAI-2K score ≤ 4, no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, or fever), no hemolytic anemia or gastrointestinal activity, and no new lupus activity since the previous assessment. Additionally, patients must have a PGA score ≤ 1, a current prednisolone dose ≤ 7.5 mg/day, and be on well-tolerated standard maintenance doses of immunosuppressants[9]. Minimizing lupus activity through the use of effective immunosuppressive agents with minimum adverse events, prevention of flares, and thereby limiting organ damage, could lead to improved outcomes and prognosis[32,33].

The introduction of new biologic agents and small molecules has marked a major milestone in SLE management. Updated EULAR recommendations cite high-quality evidence supporting the efficacy of biologic agents and recommend their use in the early stages of the disease[7]. Belimumab, in particular, has demonstrated superior results in reducing disease activity, enabling steroid tapering, and preventing flares[29,31]. New treatment options for lupus nephritis (such as belimumab and voclosporin) have also been associated with better disease outcomes[7,34]. Anifrolumab (ANI) has shown rapid and robust effects in refractory cutaneous lupus[35,36]. The four-step management approach for SLE is illustrated in Figure 1.

Tapering and discontinuation of steroids

Glucocorticoids (GCs) are widely used for SLE treatment, and a significant proportion of patients continue to receive GCs even after achieving remission. Serological activity, prior disease severity, and duration of remission are the main factors influencing this decision. However, in contrast to ANCA-associated vasculitis, high-quality RCTs assessing different tapering protocols and strategies are still lacking[37].

The KDIGO guidelines recently provided updated recommendations for the management of lupus nephritis, including detailed guidance on the initial dosing and tapering of GCs according to renal severity throughout the disease course[34]. According to EULAR, in SLE patients who have achieved sustained

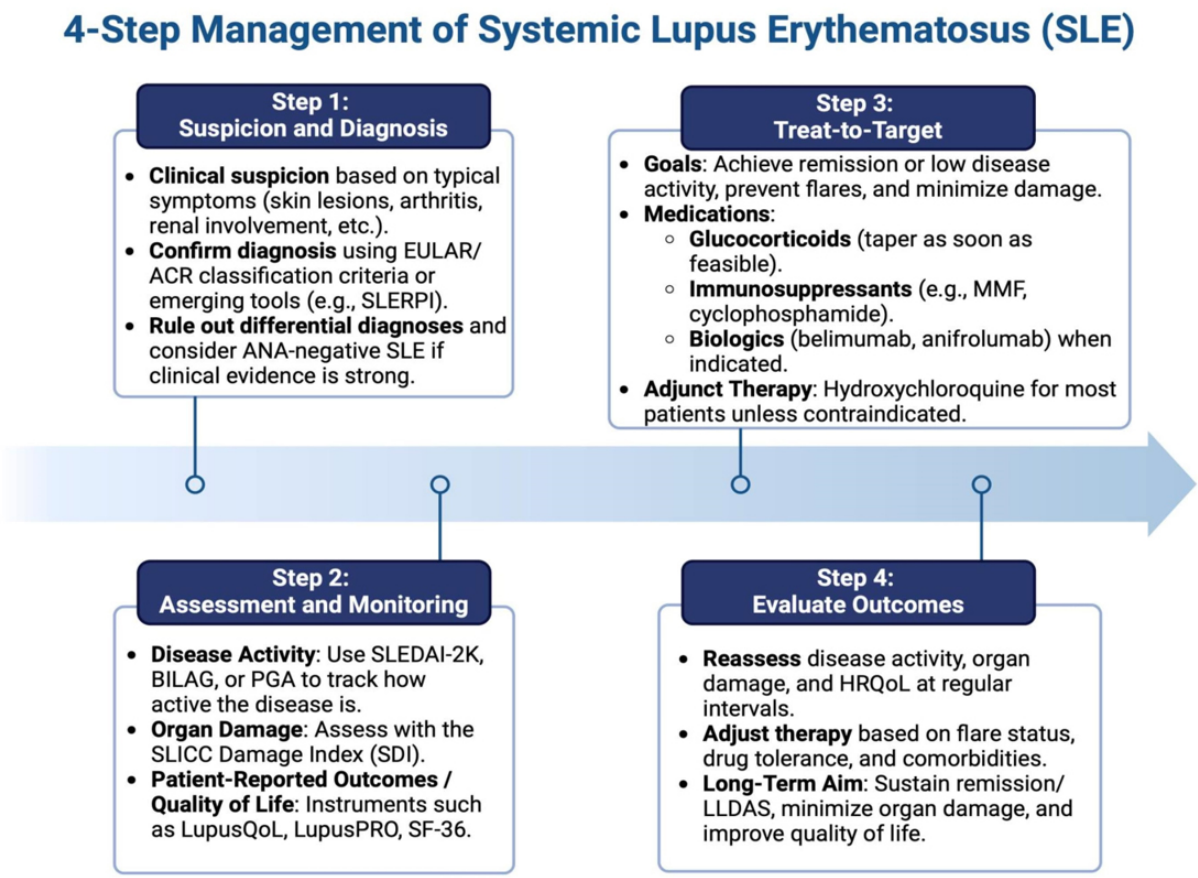

Figure 1. Management Strategy for SLE.

remission, gradual tapering of treatment should be attempted, starting with the withdrawal of glucocorticoids[7].

Two randomized trials, CORTICOLUP and WIN-LUPUS, investigated GC discontinuation (CORTICOLUP) and interruption of immunosuppressive agents (WIN-LUPUS) in extrarenal SLE and LN, respectively[38-40]. Although both studies reported higher relapse rates among patients who discontinued treatment, they paved the way for further research in this area. Tani *et al.* showed that both GC tapering and complete withdrawal are achievable and sustainable in certain lupus patients[41]. Additionally, data from the large Hopkins Lupus Cohort have shown that GC use is strongly associated with cumulative organ damage[26].

GC discontinuation should be considered in patients who have achieved long-term remission or are in a LLDAS, as this may protect against flares[41]. A gradual tapering schedule over 6 months - from 7.5 mg/day prednisone equivalent to complete withdrawal - has been associated with a reduced risk of flares[42]. In contrast, abrupt GC discontinuation, even at low maintenance doses and without concurrent immunosuppressive therapy, was linked to higher relapse rates in the CORTICOLUP trial[38]. Combining LLDAS or DORIS remission achievement, GC tapering over more than 6 months until withdrawal, and the use of HCQ has been shown to reduce overall flares by ~25-fold and severe flares by ~50-fold, while also protecting against organ damage[42]. Early use of immunosuppressants/ immunomodulators may also facilitate achieving remission.

The reduction in severe flares and successful GC tapering observed with belimumab use suggests potential efficacy in reducing long-term damage, thereby improving health-related quality of life[29,31]. Flouda *et al.* demonstrated a rapid effect of ANI in refractory cutaneous SLE and a significant reduction in GC use during follow-up[36].

In our daily clinical practice, we follow EULAR recommendations, initiating treatment with intravenous pulses of methylprednisolone for moderate to severe disease activity in combination with early immunosuppressant use, followed by oral GCs tapered and ultimately discontinued after 12 months if remission is achieved. A short-term course of GCs combined with immunosuppressive agents may also be considered for controlling lupus flares.

Tapering and discontinuation of immunosuppressive therapy and treatment of refractory disease

Complete withdrawal of treatment in SLE remains a challenging goal. As outlined above, achieving DORIS remission or LLDAS, along with preventing flares, are the main treatment objectives and are strongly associated with the use of immunosuppressive agents[43,44]. However, long-term use of immunosuppressants can lead to severe adverse events, resulting in irreversible organ damage, increased morbidity, and mortality[45].

The EULAR recommends considering gradual tapering of immunosuppressants in patients who have achieved sustained remission[7]. Nevertheless, after tapering treatment, approximately one-quarter of SLE patients may experience renal or systemic flares[45,46]. Therefore, the decision to discontinue immunosuppressive therapy should be based on a prolonged absence of disease activity and the absence of predictors for flares[38].

In lupus nephritis, Moroni *et al.* showed that complete withdrawal of immunosuppressants, including mycophenolate monotherapy, is feasible in patients who have remained relapse-free for at least four years and are in deep remission[47]. Repeated kidney biopsies in selected patients can support histological evaluation of treatment response and inform decisions on therapy discontinuation in those with both clinical and histological remission[48].

The WIN-Lupus trial was an investigator-initiated, multicenter, randomized controlled study. Patients receiving maintenance immunosuppressive therapy (IST) with azathioprine or mycophenolate mofetil for 2-3 years, along with hydroxychloroquine, were randomized (1:1) to either continue or discontinue IST. In this study, patients who discontinued IST had a higher risk of severe SLE flares[40].

The use of HCQ plays a crucial role in preventing flares and improving survival rates; therefore, it should be maintained in lupus patients unless unacceptable side effects occur[7]. A slow and gradual withdrawal of lupus therapy in patients with sustained remission and no risk factors for relapse, combined with continued HCQ use and careful medical monitoring, is recommended to minimize the risk of disease flares [Figure 2].

CD19 chimeric antigen receptor (CAR) T-cell therapy has shown promise for refractory SLE. Müller *et al.* reported achieving remission in a small group of patients with refractory disease, who were also able to discontinue their immunosuppressive medications without relapses or disease worsening[49].

CONCLUSION

SLE is a lifelong disease characterized by multiple challenges affecting various organs at different time points. Successfully managing these challenges is essential to reduce morbidity and improve patients' quality

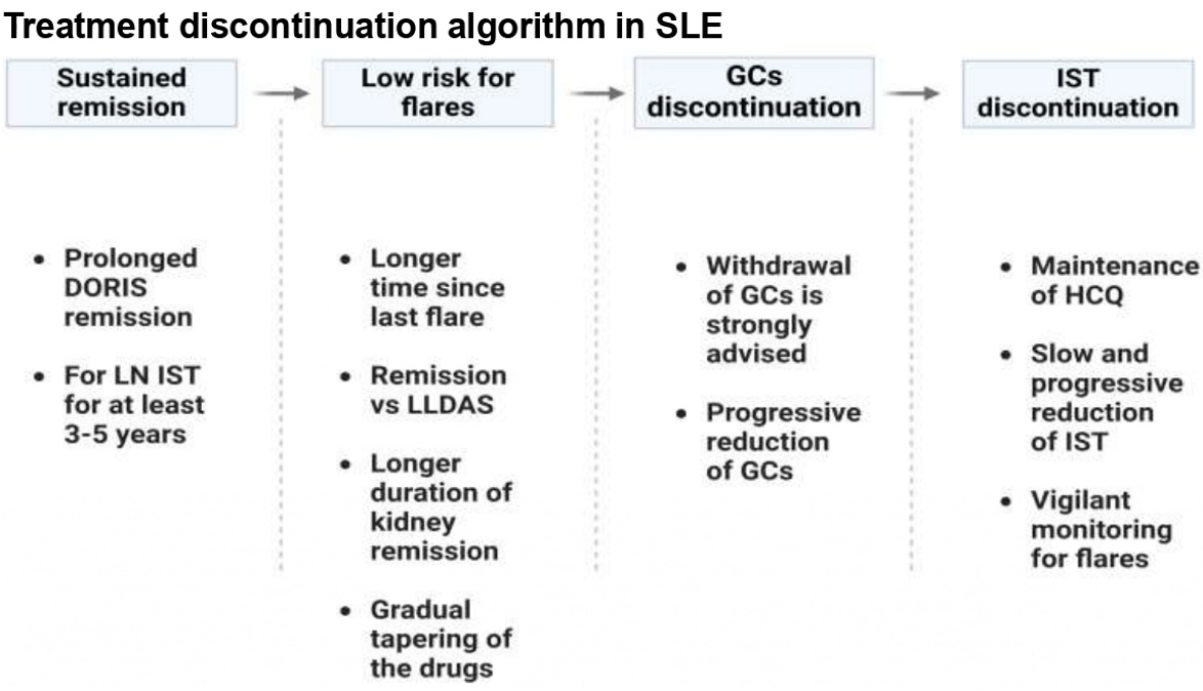

Figure 2. Treatment discontinuation in SLE. LN: Lupus nephritis; IST: immunosuppressive therapy; LLDAS: low lupus disease activity; GCs: glucocorticoids; HCQ: hydroxychloroquine.

of life. Recent additions to treatment options, including both biologic and non-biologic agents, have enabled glucocorticoid tapering without increased disease activity, reduced flare frequency, decreased organ damage, and enhanced quality of life. Early diagnosis using tools such as the SLERPI score in patients suspected of having an underlying autoimmune rheumatic disease, along with regular assessment of clinical and serological disease activity and annual evaluation of organ damage, is crucial. Timely administration of steroids and new therapies plays a vital role in disease management. For patients with severe lupus, advanced B-cell-depleting therapies may offer additional benefits beyond current immunosuppressive treatments. CD19-directed CAR T-cell therapy shows promise as an effective option for refractory SLE, even in cases previously treated with B-cell-targeting monoclonal antibodies. Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, depletes B cells more efficiently than rituximab. In the REGENCY trial, obinutuzumab combined with standard therapy demonstrated superior efficacy compared to standard therapy alone in achieving complete renal response among adults with active lupus nephritis[50].

DECLARATIONS

Authors' contributions

Data curation, visualization: Flouda S

conceptualization, Formal analysis, investigation, methodology, writing-original draft: Flouda S, Boumpas D

Project administration, writing-review and editing: Boumpas D

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Not applicable.

Consent for publication
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REFERENCES

1. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. *Ann Rheum Dis.* 2021;80:14-25. DOI PubMed
2. Tselios K, Gladman DD, Touma Z, Su J, Anderson N, Urowitz MB. Disease course patterns in systemic lupus erythematosus. *Lupus.* 2019;28:114-22. DOI PubMed
3. Tselios K, Gladman DD, Sheane BJ, Su J, Urowitz M. All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013). *Ann Rheum Dis.* 2019;78:802-6. DOI PubMed
4. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine.* 2003;82:299-308. DOI
5. Adamichou C, Genitsaridi I, Nikolopoulos D, et al. Lupus or not? SLE risk probability index (SLERPI): a simple, clinician-friendly machine learning-based model to assist the diagnosis of systemic lupus erythematosus. *Ann Rheum Dis.* 2021;80:758-66. DOI PubMed PMC
6. Ugarte-Gil MF, Acevedo-Vásquez E, Alarcón GS, et al. The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: data from a multiethnic Latin American cohort. *Ann Rheum Dis.* 2015;74:1019-23. DOI
7. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis.* 2024;83:15-29. DOI
8. Siegel CH, Sammaritano LR. Systemic lupus erythematosus: a review. *JAMA.* 2024;331:1480-91. DOI
9. van Vollenhoven R, Askanase AD, Bomback AS, et al. Conceptual framework for defining disease modification in systemic lupus erythematosus: a call for formal criteria. *Lupus Sci Med.* 2022;9:e000634. DOI PubMed PMC
10. Lin A, Wakhlu A, Connelly K. Disease activity assessment in systemic lupus erythematosus. *Front Lupus.* 2024;2:1442013. DOI
11. Gordon C, Sutcliffe N, Skan J, Stoll T, Isenberg DA. Definition and treatment of lupus flares measured by the BILAG index. *Rheumatology.* 2003;42:1372-9. DOI PubMed
12. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint European league against rheumatism and European renal association-European dialysis and transplant association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis.* 2020;79:713-23. DOI
13. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the systemic lupus international collaborating clinics/American college of rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum.* 1996;39:363-9. DOI
14. Gladman DD, Goldsmith CH, Urowitz MB, et al. The systemic lupus international collaborating clinics/American college of rheumatology (SLICC/ACR) damage index for systemic lupus erythematosus international comparison. *J Rheumatol.* 2000;27:373-6. PubMed
15. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. *Arthritis Rheum.* 1991;34:937-44. DOI PubMed
16. Adamichou C, Bertsias G. Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. *Mediterr J Rheumatol.* 2017;28:4-12. DOI PubMed PMC
17. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med.* 2005;353:2550-8. DOI
18. Ruperto N, Hanrahan LM, Alarcón GS, et al. International consensus for a definition of disease flare in lupus. *Lupus.* 2011;20:453-62. DOI
19. Isenberg DA, Allen E, Farewell V, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. *Ann Rheum Dis.* 2011;70:54-9. DOI

20. Thanou A, Chakravarty E, James JA, Merrill JT. How should lupus flares be measured? Deconstruction of the safety of estrogen in lupus erythematosus national assessment-systemic lupus erythematosus disease activity index flare index. *Rheumatology.* 2014;53:2175-81. DOI PubMed PMC
21. Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology.* 2005;44:902-6. DOI
22. Nguyen MH, Huang FF, O'Neill SG. Patient-reported outcomes for quality of life in SLE: essential in clinical trials and ready for routine care. *J Clin Med.* 2021;10:3754. DOI PubMed PMC
23. Tsoi A, Gomez A, Boström C, et al. Efficacy of lifestyle interventions in the management of systemic lupus erythematosus: a systematic review of the literature. *Rheumatol Int.* 2024;44:765-78. DOI PubMed PMC
24. Gomez A, Parodis I. Do biological agents improve health-related quality of life in patients with systemic lupus erythematosus? Results from a systematic search of the literature. *Autoimmun Rev.* 2022;21:103188. DOI PubMed
25. Mahieu M, Yount S, Ramsey-Goldman R. Patient-Reported outcomes in systemic lupus erythematosus. *Rheum Dis Clin North Am.* 2016;42:253-63. DOI PubMed PMC
26. Petri MA, van Vollenhoven RF, Buyon J, et al. Baseline predictors of systemic lupus erythematosus flares: data from the combined placebo groups in the phase III belimumab trials. *Arthritis Rheum.* 2013;65:2143-53. DOI
27. Almeida-Brasil CC, Hanly JG, Urowitz M, et al. Flares after hydroxychloroquine reduction or discontinuation: results from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort. *Ann Rheum Dis.* 2022;81:370-8. DOI
28. Garg S, Chewning B, Hutson P, Astor BC, Bartels CM. Reference range of hydroxychloroquine blood levels that can reduce odds of active lupus and prevent flares. *Arthritis Care Res.* 2024;76:241-50. DOI PubMed PMC
29. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med.* 2020;383:1117-28. DOI
30. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2011;63:3918-30. DOI PubMed PMC
31. Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. *Arthritis Rheumatol.* 2017;69:1016-27. DOI PubMed PMC
32. van Vollenhoven RF, Mosca M, Bertsias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis.* 2014;73:958-67. DOI
33. Parra Sánchez AR, Voskuyl AE, van Vollenhoven RF, et al. Treat-to-target in systemic lupus erythematosus: advancing towards its implementation. *Nat Rev Rheumatol.* 2022;18:146-57. DOI PubMed
34. Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 clinical practice guideline for the management of LUPUS NEPHRITIS. *Kidney Int.* 2024;105:S1-69. DOI PubMed
35. Ríos-Garcés R, Espinosa G, van Vollenhoven R, Cervera R. Treat-to-target in systemic lupus erythematosus: where are we? *Eur J Intern Med.* 2020;74:29-34. DOI PubMed
36. Flouda S, Emmanouilidou E, Karamanakos A, et al. Anifrolumab for systemic lupus erythematosus with multi-refractory skin disease: a case series of 18 patients. *Lupus.* 2024;33:1248-53. DOI
37. Kostopoulou M, Mukhtyar CB, Bertsias G, Boumpas DT, Fanouriakis A. Management of systemic lupus erythematosus: a systematic literature review informing the 2023 update of the EULAR recommendations. *Ann Rheum Dis.* 2024;83:1489-501. DOI PubMed PMC
38. Mathian A, Pha M, Haroche J, et al. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial. *Ann Rheum Dis.* 2020;79:339-46. DOI
39. Jourde-Chiche N, Costedoat-Chalumeau N, Baumstarck K, et al. Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial. *Ann Rheum Dis.* 2022;81:1420-7. DOI PubMed PMC
40. Ngamjanyaporn P, McCarthy EM, Sergeant JC, et al. Clinicians approaches to management of background treatment in patients with SLE in clinical remission: results of an international observational survey. *Lupus Sci Med.* 2017;4:e000173. DOI PubMed PMC
41. Tani C, Elefante E, Signorini V, et al. Glucocorticoid withdrawal in systemic lupus erythematosus: are remission and low disease activity reliable starting points for stopping treatment? A real-life experience. *RMD Open.* 2019;5:e000916. DOI PubMed PMC
42. Katechis S, Pitsigavdaki S, Nikoloudaki M, et al. Combination of clinical factors predicts successful glucocorticoid withdrawal in systemic lupus erythematosus (SLE): results from a multicentre, retrospective cohort study. *RMD Open.* 2025;11:e005118. DOI PubMed PMC
43. Van Vollenhoven RF, Bertsias G, Doria A, et al. 2021 DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med.* 2021;8:e000538. DOI
44. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis.* 2016;75:1615-21. DOI
45. Nguyen Y, Costedoat-Chalumeau N. Tapering or discontinuing SLE treatments: when and how? *Lancet Rheumatol.* 2023;5:e566-7. DOI PubMed
46. Zen M, Saccon F, Larosa M, Gatto M, Iaccarino L, Doria A. 173 immunosuppressant discontinuation in systemic lupus erythematosus: prevalence, risk of subsequent flare and effect on damage accrual. *Rheumatol Oxford.* 2020;59:1591-8. DOI
47. Moroni G, Frontini G, Ponticelli C. When and how is it possible to stop therapy in patients with lupus nephritis: a narrative review.

Clin J Am Soc Nephrol. 2021;16:1909-17. DOI PubMed PMC

48. Malvar A, Alberton V, Lococo B, et al. Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. *Kidney Int.* 2020;97:156-62. DOI
49. Müller F, Taubmann J, Bucci L, et al. CD19 CAR T-cell therapy in autoimmune disease - a case series with follow-up. *N Engl J Med.* 2024;390:687-700. DOI
50. Furie RA, Rovin BH, Garg JP, et al. Efficacy and safety of obinutuzumab in active lupus nephritis. *N Engl J Med.* 2025;392:1471-83. DOI