Review

Systemic lupus erythematosus: one year in review 2026

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by a complex pathogenesis, heterogeneous clinical manifestations and a variable disease course. This review summarises the most relevant contributions on SLE published during 2025, following the framework of the One Year in Review series. In particular, we focus on emerging pathogenetic insights, novel and refined biomarkers, clinical manifestations and outcomes, comorbidities, and evidence from clinical trials and real-world studies, highlighting both recent progress and persistent unmet needs in the management of SLE.

Introduction

In line with the previous annual reviews of this series (1, 2), we performed a MEDLINE search of English-language articles published between 1st January and 31st December 2025, using MeSH terms and free-text words related to systemic lupus erythematosus (SLE). Original articles focusing on adult SLE were selected, while case reports were excluded. We have summarised the most relevant contributions published during 2025, with a focus on pathogenetic insights, biomarkers, clinical manifestations and outcomes, comorbidities, and emerging therapeutic strategies, following the established framework of the *One Year in Review* series.

Pathogenesis and new treatment targets

In 2025, original experimental and translational studies further advanced the understanding of SLE pathogenesis by shifting the focus from single dominant pathways to spatially defined immune circuits operating within target tissues.

Type I interferon (IFN) remains a central driver of immune dysregulation in SLE. However, recent works have refined this paradigm by demonstrating that IFN-driven pathology is highly context-dependent and locally sustained within target tissues. In this regard, Wang *et al*. (3) identified a previously unrecognised population of cytotoxic interferon-stimulated gene-expressing T cells (ISG-T cells) that may contribute to autoimmune kidney damage in SLE. In kidney tissue, type I IFN induced the transcription factor IRF7 in T cells, promoting granzyme B expression and cytotoxic function in both $CD8^+$ and $CD4^+$ T cells. (3) This spatial view of IFN signalling may help explain heterogeneous clinical responses to systemic IFN blockade and suggests that locally maintained immune circuits may require complementary or upstream therapeutic interventions.

Extending this tissue-centred perspective, studies in lupus nephritis (LN) identified a lupus-specific inflammatory niche in the renal cortex characterised by the co-localisation of immune cells, myofibroblasts, and a distinct population of $VCAM1^+$ tubular epithelial cells. These epithelial cells appear to arise from a failed repair program and display pro-inflammatory and profibrotic features, potentially sustaining tissue injury and progression. By integrating SLE genome-association study data, the authors directly linked genetic susceptibility to pathogenic epithelial cells in LN (4).

Beyond inflammatory niches, additional single-cell and spatial analyses highlighted profibrotic cellular trajectories and signalling networks that were partially independent of inflammatory immune infiltrates and immune complex deposition (5). Collectively, these observations reinforce the concept that renal fibrosis in LN is not merely a passive consequence of unresolved inflammation, but an active, biologically regulated process contributing to irrevers-

ible damage. Consistent with this view, additional tissue-based evidence has highlighted the relevance of intracellular inflammatory and stress-response pathways within the kidney. In renal biopsy specimens from patients with active LN, increased expression of NF-κB and its molecular chaperone HSP90 was observed and correlated with clinicopathological indices, supporting a role for sustained intrarenal inflammatory signalling in disease activity and progression (6).

While these studies emphasise organ-level immune circuits, upstream innate activation remains a critical driver of systemic immune amplification. Aberrant RNA-sensing pathways, particularly those mediated by Toll-like receptors 7 and 8 (TLR7/8), have emerged as a key upstream mechanism amplifying innate immune activation in SLE. KBD4466 is a novel small-molecule inhibitor that selectively targets Toll-like receptors 7 and 8 (TLR7/8). Through chemistry optimisation, it showed potent inhibition of TLR7/8-mediated cytokine production *in vitro* and effectively reduced disease manifestations in an established murine lupus model (7).

The growing understanding of pathogenic immune compartments has also paved the way for therapeutic strategies aimed at their selective eradication. Among these, chimeric antigen receptor (CAR) T-cell therapy has emerged as a particularly promising cellular immunotherapy approach in systemic autoimmune diseases. By redirecting cytotoxic T cells toward defined B-cell or plasma cell populations, CAR T-cell therapy enables selective depletion of immune compartments that are resistant to standard immunosuppression and B-cell depletion. Early interventional studies reported deep B-cell depletion across tissues, including secondary lymphoid organs and inflamed target tissues, with subsequent reconstitution of a more naive and less autoreactive immune repertoire. Beyond therapeutic potential, CAR T-cell approaches may also provide a mechanistic tool to probe the contribution of persistent humoral immunity to disease chronicity (8, 9).

In line with this concept, a major therapeutic advance reported in 2025 was the demonstration that selective targeting of antibody-secreting cells can induce profound and sustained clinical remission in refractory LN (8). B-cell maturation antigen (BCMA) is expressed on antibody-secreting cells as well as on selected subsets of mature B cells, highlighting its potential as a therapeutic target for B-cell and plasma cell depletion strategies. In an open-label clinical study, BCMA-targeted CAR T-cell therapy induced rapid depletion of pathogenic plasma cells, leading to marked clinical and serological improvement. Importantly, the ability of BCMA-directed targeting to induce deep and durable remission supports a central pathogenic role for long-lived antibody-secreting cells, which are largely resistant to conventional B-cell-directed approaches that may have limited penetration into tissues and do not effectively eliminate autoantibody-secreting populations (8).

Take-home messages

- Distinct but interacting immune circuits, including interferon signalling, RNA-sensing pathways, pathogenic T-B cell collaboration, humoral immune persistence, and tissue-specific remodelling programs, coexist within individual patients and contribute variably to disease manifestations (3-5, 7-9).
- This framework provides a strong biological rationale for mechanism-based patient stratification and for the development of rational combination therapies targeting dominant pathogenic modules (3, 4, 8).

Biomarkers

SLE complexity highlights the critical need for robust biomarkers to enable disease stratification, monitor activity, and predict long-term outcomes.

Recent evidence has identified soluble immune checkpoint molecules as promising biomarkers in SLE. In a large cohort study (10), elevated serum levels of sCD25, sTim-3, and sGal-9 were consistently associated with active disease and identified a subgroup of patients with a more severe clinical phenotype. Among the analysed molecules, sCD25 uniquely correlated with sustained DORIS remission and low disease activity state (LLDAS), highlighting its potential utility as a predictor of long-term disease control and treatment de-escalation.

In addition, reduced serum levels of NLRC3, a negative regulator of innate immune activation, were reported in patients with active SLE compared with those in LLDAS and healthy controls. Lower NLRC3 levels were associated with selected clinical manifestations and complement consumption, suggesting that impaired counter-regulatory innate pathways may parallel inflammatory activity in SLE (11).

Beyond disease activity and prognosis, recent studies have emphasised the importance of biomarkers able to predict response to targeted therapies. In this context, McCluskey *et al*. (12) identified serum IgA2 anti-dsDNA antibodies as a validated theragnostic biomarker for response to sequential B cell–targeted therapy with rituximab followed by belimumab. Across two independent clinical trials (BEAT-lupus and CALIBRATE), high baseline IgA2 anti-dsDNA levels identified a subset of patients more likely to respond to belimumab after rituximab compared with rituximab alone. Mechanistically, rituximab-induced B cell depletion leads to a compensatory increase in BAFF levels, which preferentially supports the survival and activation of IgA2-producing plasmablasts due to their higher expression of the BAFF receptor. In patients with elevated IgA2 anti-dsDNA antibodies, this BAFF-dependent pathway sustains autoantibody production and disease activity, whereas subsequent BAFF blockade with belimumab selectively targets these cells, resulting in reduced IgA2 autoantibody levels and improved clinical outcomes.

Cellular biomarkers have also gained attention. A recent study showed that circulating plasmablast proportions were strongly associated with disease activity, correlating with SLEDAI-2K scores, anti-dsDNA titres and complement consumption. Moreover, dynamic monitoring suggested that persistently elevated plasmablast levels may identify patients with suboptimal treatment response, supporting their potential role

as a complementary biomarker for disease monitoring (13).

In parallel, increasing interest has focused on microRNAs (miRNAs) as emerging biomarkers that integrate molecular mechanisms with clinical phenotypes in SLE (14). A recent systematic review and meta-analysis demonstrated that circulating miRNAs show good diagnostic accuracy for LN, with miR-181a, miR-223, and miR-146a emerging as the most promising candidates (14).

LN represents one of the most severe manifestations of SLE and an area where reliable biomarkers are particularly needed. In this context, recent advances in ultrasensitive proteomic technologies have enabled direct quantification of circulating interferon proteins, overcoming some of the limitations of transcriptomic interferon signatures. Using a high-sensitivity approach, Huang *et al*. (15). measured multiple type I, II and III interferon proteins in a large SLE cohort and demonstrated that type I interferons (IFNα1:IFNα13, IFNα2 and IFNω), together with type III interferons, but not IFNβ or IFNγ, were consistently associated with disease activity, serological markers and lupus nephritis.

Gavin *et al*. (16) investigated the modulation of the LN metabolome following type I interferon receptor (IFNAR1) blockade with anifrolumab. Untargeted serum and urine metabolomic analyses identified indoxyl sulfate (IS) as a serum metabolite influenced by anifrolumab therapy. Elevated baseline IS levels correlated with baseline creatinine levels and the NIH chronicity index, whereas improvement in renal function was associated with lower IS levels, suggesting a potential role for IS as a non-invasive biomarker of renal disease progression and chronic damage. *In vitro* IS exposure increased endothelial ICAM-1 and VCAM-1 expression, supporting a role in glomerular endothelial dysfunction. Additionally, pyrimidine metabolites were reduced after anifrolumab treatment and urinary pyrimidine levels correlated with disease activity and type I interferon pathway activation.

Alpha interferon (IFN-α) may also represent a potential disease biomarker. Its measurement has been limited by low circulating serum levels; however, González-Gay *et al*. (17). quantified serum IFN-α and IFN-γ using a novel ultrasensitive assay. Disease activity assessed by SLEDAI was significantly associated with higher IFN-α levels compared with no disease activity, whereas this association was not observed when comparing mild activity with inactive disease. By contrast, according to the SLE-DAS score, mild disease activity showed a significant multivariable association with higher IFN-α levels compared with remission, while moderate or severe activity did not. Conversely, remission as defined by the DORIS criteria and LLDAS showed significant and independent negative associations with IFN-α levels. Using an ultrasensitive approach, circulating interleukin-8 was also evaluated as a potential biomarker in SLE. In a well-characterised cohort, serum IL-8 levels showed no association with disease activity indices or autoantibody profiles. However, IL-8 concentrations correlated with cardiovascular risk parameters, supporting the concept that selected inflammatory mediators may primarily reflect comorbidity burden rather than immune-mediated disease activity (18).

Progress has also been made in biomarker-driven models for neuropsychiatric involvement. A recent study proposed a clinical nomogram incorporating serum sTREM2, a marker linked to microglial activation, which showed good discriminative performance for neuropsychiatric SLE. Although external validation is required, these findings support the integration of mechanistic biomarkers with clinical variables to improve risk stratification in complex SLE subphenotypes (19).

Take-home messages

- Soluble immune checkpoints, notably sCD25, correlate with disease activity and organ-specific involvement in SLE and may predict sustained remission and treatment de-escalation (10).
- Therapeutic stratification biomarkers, such as IgA2 anti-dsDNA, identify distinct immune endotypes responsive to sequential B-cell-targeted therapies (12).
- Molecular and metabolic signatures, including specific microRNAs and metabolites like indoxyl sulfate, hold promise for diagnosing organ involvement and monitoring disease progression, although standardisation challenges remain (14, 16).

Clinical aspects and outcomes

Treat-to-target (T2T) strategies in SLE have been recommended for over a decade, aiming to achieve and sustain remission or LLDAS. Within this framework, a clear understanding of physicians' diagnostic pathways and therapeutic priorities is essential. A physician-based discrete-choice experiment showed that lupus-treating clinicians are highly aware of the unmet need for early diagnosis and prevention of irreversible damage accrual (20). Despite this awareness, a substantial proportion of patients still fail to reach T2T targets and remain at risk of adverse outcomes. Recognition of this unmet need has prompted efforts to better define severe, treatment-refractory disease. A multinational Asia-Pacific cohort proposed a pilot definition of severe refractory SLE, identifying patients with persistently high disease activity (SLEDAI-2K ≥10) despite combined glucocorticoid and immunosuppressive therapy. Among 3,744 patients, 14% met criteria for refractory SLE; fewer than 25% achieved LLDAS and only 1% reached glucocorticoid-free remission over 12 months (21). These findings are complemented by recent analyses of severe flares (22). A clustering study identified three distinct flare phenotypes: two predominantly extra-renal clusters and one renal cluster. One extra-renal cluster was characterised by severe constitutional symptoms, serositis, and arthritis in younger patients, associated with hyperinflammatory biomarkers and multiple autoantibody specificities. The second extra-renal cluster included flares dominated by mucocutaneous and musculoskeletal manifestations, frequently associated with antiphospholipid syndrome. Notably, in the hyperinflammatory extra-renal cluster, only approximately 50% of flares achieved LLDAS and about 35% reached remission at 12 months, highlighting that a substantial proportion of patients remained non-

responsive to standard therapy, similar to what was observed in the renal cluster (22).

Renal involvement remains one of the most clinically impactful manifestations of SLE. A retrospective cohort study with independent validation identified younger age at SLE diagnosis, male sex, and serological activity as strong predictors of subsequent kidney involvement (23). Beyond disease onset, a study from the Toronto Lupus Cohort further clarified the prognostic role of baseline proteinuria in LN. Higher proteinuria at presentation was associated with an increased risk of adverse renal endpoints and flares. Importantly, low-level proteinuria did not indicate benign disease: nearly 60% of patients with proteinuria ≤1 g/day already had proliferative lesions on biopsy, and over one-quarter experienced adverse renal outcomes during follow-up (24).

In parallel, the concept of remission in LN has been further refined. A longitudinal study demonstrated that a minimum of three years of sustained clinical remission, defined by stable estimated glomerular filtration rate, proteinuria <0.5 g/day, and absence of systemic disease activity, was required to significantly reduce the risk of impaired kidney function (HR 0.10, 95%CI 0.04–0.29, $p<0.001$) and organ damage accrual (25).

For neuropsychiatric SLE, two recent studies have underscored both the dynamic nature of cognitive impairment (CI) and the role of imaging in guiding clinical assessment. Prospective data from the Toronto Lupus Cohort characterised cognitive impairment (CI) over a 1-year period: approximately 17% of patients had persistent CI, 29% fluctuated, and the remainder remained stable. Persistent CI was more severe and preferentially affected memory, attention, processing speed, and visuospatial domains (26). In the field of neuroimaging, a multicentre retrospective MRI study found that conventional brain MRI was useful in supporting the attribution process: normal imaging and cerebral atrophy predominated in non-attributed cases, whereas inflammatory-type lesions were more frequent in SLE-attributed events (27).

Finally, a substantial unmet need persists in the management of rare SLE manifestations, largely due to their low prevalence and limited evidence base. The ERN ReCONNET SLICC SLEuro expert consensus offered a pragmatic framework for the management of rare and severe SLE phenotypes for selected haematological, gastrointestinal, pulmonary, cutaneous, retinal, and neurological manifestations, as well as thrombotic microangiopathy defining treatment strategies stratified according to disease severity (28).

Take-home messages

- Despite T2T implementation in SLE, approximately 14% meeting pilot criteria for severe refractory SLE (21) and 50% with hyperinflammatory or renal severe flares (22), failed to achieve optimal disease control, highlighting persistent therapeutic gaps.
- In LN, new evidence suggests that even low-level proteinuria is associated with proliferative LN and adverse long-term outcomes, whereas ≥3 years of sustained remission strongly protects against impaired kidney function (24, 25).
- Rare and severe SLE manifestations remain challenging; the ERN ReCONNET SLICC SLEuro consensus offers organ- and severity-stratified guidance to support treatment decisions (28).

Comorbidities and organ damage

Comorbidities screening, monitoring, and control, as well as organ damage prevention, are cornerstones of SLE management, as confirmed by sets of international recommendations published in 2025. The 2025 American College of Rheumatology (ACR) Guidelines for the Treatment of SLE include general suggestions addressing cardiovascular (CV), infectious and neoplastic conditions, clearly underlining that comorbidities management should be incorporated into SLE care (29). Since SLE is a multifaceted disease, the need for multidisciplinary collaboration between rheumatologists and the relevant specialists is highlighted, particularly when procedures extend beyond routine rheumatology practice.

Even the 2025 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of SLE with kidney involvement strongly supports this message (30). The authors encourage rheumatology-nephrology interdisciplinary care teams to ensure improved outcomes, aiming to prevent flares, damage accrual and progression to chronic kidney disease (CKD), address comorbidities and improve quality of life.

Given the complexity of the disease, the relationship between comorbidities and clinical characteristics is of utmost importance in SLE. Exploiting a multicenter retrospective cohort study (RELESSER-TRANS) including 3,658 patients, Rua-Figueroa *et al*. (31). performed a cluster analysis to evaluate the associations between comorbid conditions (depression, CV events, infections) and clinical characteristics. The cluster characterised by the absence of key comorbidities shared lower rates of damage accrual, treatment refractoriness and mortality, whereas clusters with CV events were associated with higher damage and mortality (31). These findings support the need to include comorbidities in disease phenotyping, since the most relevant comorbidities aggregate in the most severe patients' subsets.

Beyond clinical clustering, emerging data suggest that comorbidity aggregation may reflect shared biological mechanisms across systemic autoimmune diseases. A transcriptomic multicohort analysis comparing SLE and rheumatoid arthritis identified overlapping immune-regulatory pathways, including interferon-related and innate immune signalling circuits, supporting the concept of partially convergent pathogenic endotypes across systemic rheumatic diseases (32). Importantly, comorbidity burden in SLE is increasingly captured by integrative outcomes rather than single organ involvement. In this context, frailty has emerged as a clinically relevant construct reflecting cumulative vulnerability. A recent study identified depressive symptoms and reduced social support as independent risk factors for frailty in SLE, highlighting the contribution of psychosocial and non-inflammatory determinants to ad-

verse outcomes and reinforcing the need for multidimensional patient assessment (33).

Moreover, given the growing availability of molecules to treat comorbid conditions, rheumatologists should acquire proficiency in using non-rheumatological drugs. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) demonstrated positive effects on CV risk and progression to CKD. Adopting a large, insurance-based cohort from the United States using propensity score matching, 2,165 SLE patients suffering from T2D starting SGLT2i were compared with 2,165 SLE subjects receiving dipeptidyl peptidase-4 inhibitors (DPP4i), a class of drugs which did not demonstrate CV and kidney outcomes improvement in T2D (34). After a mean follow-up period of over 700 days, mortality rates were similar, but SGLT2i-treated patients had lower CKD and heart failure risks. This suggests that the renal and CV benefits of SGLT2i in T2D safely translate to patients with SLE, supporting the further development of this non-immunological treatment as add-on therapy.

Damage accrual prevention is an essential point to define disease modification in SLE. Touma *et al*. (35) performed a retrospective study comparing an anifrolumab arm, including 354 moderately- to severely active SLE patients who initiated anifrolumab plus standard-of-care in the TULIP-1 and 2 trials, with a real-world standard-of-care (RWSOC) arm from the University of Toronto Lupus Clinic. After propensity score matching to account for baseline confounders, the mean change in SDI at week 208 was 0.416 points lower for anifrolumab-treated patients versus RWSOC, with a significant increase in time to first organ damage progression.

Most studies on damage in SLE assess risk factors for overall damage, while domain-specific damage accrual is less studied. A large analysis of the Asia-Pacific Lupus Collaboration database analysed the predictors of damage accrual in specific organ domains to assess whether risk factors for overall damage overlapped with those associated with domain-specific damage accrual (36). Among 3,449 patients, risk factors differed across each organ domain and diverged from the overall damage associations; glucocorticoids associated with damage accrual in musculoskeletal, renal, neuropsychiatric, and gastrointestinal systems, while antimalarials were protective against damage in renal and pulmonary systems. Thus, domain-specific risk profiles might help clinicians anticipate organ domain–specific damage. Considering global damage prediction, instead, the SLE-Damage Risk Index (SLE-DRI) was developed as a scoring system enabling effective identification of patients at risk for early organ damage (37). Machine learning techniques were applied to an extensive set of clinical features in a derivation cohort of 914 SLE patients followed for 5 years after diagnosis and in an external validation cohort. A threshold of ≥3 in the SLE-DRI achieved an Area Under the Curve (AUC) of 0.86, overcoming the effect of classification criteria manifestations, disease activity, treatment intensification and comorbidities burden, and emerging as a feasible tool to improve patient stratification.

Take-home messages

- International recommendations reinforce the role of rheumatologists in monitoring and managing comorbidities, calling for greater uniformity in reporting and shared treatment protocols with the relevant specialists (29, 38).
- Comorbidities appear to cluster within the most severe patient subgroups and should be considered in disease phenotyping (31).
- Anifrolumab demonstrated disease-modifying activity by slowing damage accrual, confirmed through comparison with a real-world standard-of-care cohort after propensity score matching (35).

Reproductive health

Reproductive health remains a core domain in SLE, given the predominance of disease onset during childbearing age and the persistent, clinically meaningful increased risk of adverse pregnancy outcomes (APOs) compared with the general population.

Two large nationwide Swedish studies provide a contemporary view of how outcomes and management have evolved. Over two decades, temporal analyses show that SLE pregnancies continue to carry increased rates of APOs compared with the general population, but also suggest progressive improvements in pregnancy care in rheumatic disease (39). Specifically, the proportion of pregnancies complicated by pre-eclampsia declined from 14.1% in 2003-2004 to 9.6% in 2021–2022, while preterm delivery decreased from 25.9% to 11.2%. These favourable trends paralleled increased use of antimalarials, low-dose aspirin, and guideline-concordant immunosuppressive strategies, although the residual excess risk compared with the general population remained substantial (39).

In parallel, a focused nationwide cohort study on 959 SLE pregnancies evaluated early pregnancy exposure to HCQ and found associations with key obstetric endpoints (40). Early HCQ exposure was associated with a relative reduction in the risk of pre-eclampsia compared with non-exposed pregnancies.

In addition, a recent work explored how much HCQ exposure matters and whether pharmacologic variability correlates with outcomes. In a multicentre observational study on 174 patients, maternal HCQ levels during pregnancy were analysed in relation to maternofetal outcomes (41). First-trimester subtherapeutic (≤500 ng/ml) and severely non-adherent (≤200 ng/ml) HCQ levels were associated with a significantly higher risk of severe maternal flares, whereas no clear association was observed with APOs. These data support the clinical relevance of adherence assessment and, in selected high-risk patients, pharmacologic monitoring (41).

Recent updated EULAR recommendations on anti-rheumatic drug use in reproduction, pregnancy, and lactation also address the role of biologic therapies, including belimumab. While data on pregnancy exposure remain limited, belimumab may be considered in selected women with SLE when required to maintain disease control (42). This reflects a shift toward individualised, risk-benefit-based therapeutic decisions, recognising that uncontrolled disease activity itself represents a major

determinant of adverse pregnancy outcomes.

Real-world evidence from Asia further sharpens the clinical implications of treatment continuity and preconception planning. A large retrospective cohort study from Korea involving 4,880 pregnancies in 3,059 women with SLE assessed immunosuppressant use patterns from preconception through pregnancy and their association with specific APO categories (43). Continuous HCQ use was associated with a lower risk of preterm birth compared with discontinuation, late initiation, or non-use. These findings operationalise current recommendations by demonstrating that both medication continuity and timely therapeutic transitions before conception materially influence obstetric risk.

Risk stratification remains central because SLE is heterogeneous and pregnancy risk is not uniform across patients. A 13-year multicentre cohort addressed pregnancy risk stratification and subgroup analyses, contributing to a more granular approach to counselling and surveillance intensity (44). Active disease at conception, renal involvement, and hypertension emerged as dominant predictors (45). Across both cohorts, renal disease and uncontrolled activity consistently doubled the risk of composite APOs (44, 45).

Finally, the postpartum period is gaining visibility as a discrete and vulnerable phase rather than a simple 'end' to pregnancy care. A referral-centre experience focusing on postpartum outcomes in systemic autoimmune diseases, including SLE, emphasises that this phase is characterised not only by a substantial risk of disease flare but also by a non-negligible burden of additional maternal complications, including hypertension, haemorrhages and infectious complications (46). These findings underscore that the postpartum period represents a phase of compounded vulnerability, shaped by rapid immunologic and hormonal shifts and potential treatment interruptions; consequently, it is precisely the moment when the system should not 'de-intensify' care without a predefined surveillance and management plan.

Take-home messages

- Pregnancy outcomes in SLE are improving over time but remain significantly worse than in the general population, with pre-eclampsia declining from 14.1% to 9.6% and preterm delivery from 25.9% to 11.2% over two decades (39).
- Early hydroxychloroquine exposure is associated with reduced risk of pre-eclampsia (40), while subtherapeutic or non-adherent hydroxychloroquine levels during pregnancy are linked to a higher risk of severe maternal flare (41).
- Recent EULAR recommendations support a more individualised approach to biologic therapy in women with SLE of reproductive age, acknowledging that selected agents, including belimumab, may be considered when necessary to maintain disease control, given the risks associated with active disease (42).
- The postpartum period represents a phase of compounded vulnerability in SLE, with frequent disease flares and additional maternal complications, underscoring the need for structured follow-up beyond delivery (46).

Treatment: clinical trials and drug discovery

In 2025, several phase II-IV clinical studies expanded the therapeutic landscape of SLE, encompassing novel biologics, small molecules and alternative routes of administration.

Telitacicept, a dual BAFF/APRIL inhibitor, was evaluated in a phase III trial (47), demonstrating a significantly higher proportion of responders in the Telitacicept group compared with placebo, together with consistent improvements in key secondary endpoints and a clinically meaningful glucocorticoid-sparing effect. The treatment was generally well tolerated, with an acceptable safety profile. These results represent one of the most robust pieces of evidence for a new biologic agent in SLE in recent years and support Telitacicept as a new therapeutic option targeting B-cell survival pathways beyond BAFF inhibition alone.

Targeting intracellular signalling pathways was further investigated in the long-term extension of the phase II trial evaluating upadacitinib (48), alone or in combination with elsubrutinib, a Bruton tyrosine kinase inhibitor. At 104 weeks, sustained improvements in composite clinical endpoints were observed, together with maintenance of glucocorticoid dose reductions. Although the trial was not designed for direct comparison between monotherapy and combination therapy, these long-term data support the durability of clinical benefit signals of this therapeutic strategy for SLE and provide important information on prolonged exposure to it.

Additional evidence supporting the role of Janus kinase inhibition was provided by a phase II open-label study of tofacitinib in patients with active mucocutaneous disease (49). Treatment was associated with a significant improvement in cutaneous disease activity and further corroborates the biological plausibility of targeting the JAK-STAT pathway in SLE.

Among novel B cell-directed therapies, ianalumab, a monoclonal antibody targeting the BAFF receptor, was investigated in a randomised phase II study (50). Ianalumab combines receptor blockade with antibody-dependent cellular cytotoxicity, resulting in both functional inhibition and depletion of BAFF-receptor-expressing B cells. The trial showed higher clinical response rates compared with placebo and a favourable steroid-sparing effects. These results support BAFF-receptor targeting as a promising alternative to ligand-directed approaches and justify further late-phase clinical development.

The therapeutic potential of interferon pathway blockade continues to evolve with the development of alternative formulations. In 2025, a phase III randomised trial evaluated a subcutaneous formulation of anifrolumab in patients with moderate to severe SLE (51). The study met its primary clinical endpoint while maintaining a safety profile comparable to that observed with the intravenous formulation.

Finally, the phase IIb CARE trial evaluated the clinical efficacy and safety of cenerimod, a selective sphingosine-1-phosphate receptor-1 modulator, in patients with moderate to severe SLE

(52). Although the study did not meet its primary clinical endpoint, cenerimod showed consistent biological and pharmacodynamic activity supporting the scientific rationale for its further phase III development.

Take-home messages

- Dual BAFF/APRIL blockade and BAFF receptor-targeted B cell depletion with telitacicept and ianalumab showed clinically meaningful efficacy signals and relevant glucocorticoid-sparing effects in phase III and phase II randomised trials, respectively (47, 50).
- Novel therapeutic approaches targeting distinct immunological compartments are rapidly expanding, including intracellular signalling inhibition (JAK and BTK pathways), with sustained clinical benefit signals observed in medium term follow-up (48, 49).
- Optimisation of established pathways and drug delivery is also progressing, as shown by the efficacy of subcutaneous anifrolumab (51).

Treatment:
real world evidence

Beyond randomised clinical trials, recent large observational cohorts offer critical insight into real-world implementation of SLE therapies, particularly in heterogeneous and fragile patient populations underrepresented in pivotal studies.

In this context, nationwide French claims data show that nearly half of the prevalent SLE population in 2019 received oral glucocorticoids, and 12.4% had a mean daily dose exceeding 5 mg/day, a threshold associated with increased cardiovascular risk, infections and osteoporosis (53). Notably, 13.6% of patients receiving >5 mg/day were not co-treated with antimalarials, immunosuppressants or biologics, indicating underuse of steroid-sparing strategies. Similar patterns emerge from the international SPOCS cohort of patients with moderate-to-severe disease, where antimalarials (81.1%), glucocorticoids (65.0%) and immunosuppressants (54.8%) predominated, whereas only 21.2% of patients received biological therapy (54).

Beyond overall exposure, real-world studies also question traditional assumptions regarding glucocorticoid dosing in organ-threatening disease. In a multicentre cohort of new-onset biopsy-proven LN, patients initiating high-dose prednisone (>40 mg/day) accrued higher glucocorticoid exposure over the first year without improvement in 12-month complete renal response compared with those starting at ≤40 mg/day (55). Multivariable analyses confirmed that higher initial doses were not associated with better renal outcomes, suggesting that high starting doses add toxicity without clear benefit. Treatment selection in routine practice also reflects the tension between phenotype-driven strategies and real-world constraints. An Italian observational study showed that renal involvement favoured mycophenolate mofetil, musculoskeletal disease methotrexate, and higher SLEDAI scores belimumab initiation (56). However, these associations were attenuated in patients with accrued organ damage or significant comorbidity, indicating that safety considerations and patient frailty often outweigh idealised phenotype-based approaches in complex clinical scenarios. Against this background, targeted biological therapies are increasingly integrated into routine care. In a large multicentre Italian cohort with long-term follow-up, belimumab was associated with significant improvements in articular and cutaneous disease activity, with reductions in DAS28 and CLASI scores and higher remission rates, particularly in non-deforming non-erosive arthritis and acute or subacute cutaneous lupus (57).

Complementary pharmacokinetic and immunogenicity data from a Swedish observational study demonstrated wide interindividual variability in belimumab serum concentrations, though levels were stable over time at the population level (58). Anti-drug antibodies were essentially absent, and drug concentrations were only weakly associated with disease activity and not with adverse events, suggesting limited utility of routine therapeutic drug monitoring.

Along the same B-cell-targeted therapeutic axis, emerging real-world data support the use of telitacicept, particularly in LN. Add-on telitacicept therapy was associated with higher renal response rates, greater proteinuria reduction and enhanced steroid tapering compared with standard therapy alone, with a similar safety profile and more pronounced benefits in patients with class V LN and high baseline proteinuria (59).

Shifting from B-cell modulation to alternative pathways, real-world experience with type I interferon inhibition further expands steroid-sparing options. In a prospective German monocentric cohort, anifrolumab induced rapid and sustained reductions in disease activity, with significant improvements in SLE-DAI-2K and ECLAM scores within three months (60). By 12 months, over half of patients achieved DORIS remission and nearly 90% reached lupus low disease activity state (LLDAS).

For severe or refractory disease, intensified B-cell depletion strategies have been explored in real-world settings. In a Chinese series including newly diagnosed and relapsing or refractory patients, a single 1000 mg dose of obinutuzumab resulted in marked disease control (61). Among patients with LN, 86.7% achieved complete renal response, while 37.5% of the overall cohort reached DORIS remission. Mean daily glucocorticoid doses were tapered from 43 mg to approximately 9 mg/day. Additional real-world data address the safety of Voclosporin (62). Post-marketing pharmacovigilance analyses using the FDA Adverse Event Reporting System identified signals for vascular, cutaneous and gastrointestinal adverse events, as well as previously unreported events such as hypertensive urgency, hypertrichosis and gingival swelling, underscoring the need for vigilant monitoring and careful dosing in routine practice.

Finally, hydroxychloroquine remains a cornerstone of SLE management, and large observational consortia are refining precision monitoring strategies. In over 1800 patients with measured blood levels, toxicity risk increased sharply at concentrations ≥1150 ng/mL, without further disease control (63). Patients with chronic kidney disease stage ≥3

were at higher risk of reaching suprathrapeutic levels, supporting a proposed therapeutic window of 750–1150 ng/mL, particularly in patients with renal impairment.

Take-home messages

- Steroid overuse persists in real-world SLE, with many patients remaining on >5 mg/day despite disease improvement and limited benefit from high initial doses in nephritis (53-55).
- Biologics (B-cell and IFN-targeted) show meaningful effectiveness and steroid-sparing in routine practice, but comorbidity and frailty often drive treatment decisions more than phenotype (56, 57, 59-61).
- Adjunctive kidney-protective strategies and precision monitoring are emerging priorities, including vigilance for voclosporin safety signals and HCQ level-guided dosing (62, 63).

Patient-reported outcomes

Despite improved prognosis, patients with SLE continue to report poor health-related quality of life (HRQoL) (64).

According to the recommendations for the management of the disease, quality of life should be regularly assessed, and treatment goals should include optimisation of HRQoL.

New therapies show promise in improving PROs. In the last year, the results of the TULIP-LTE, a 3-year randomised, phase 3 long-term extension of the 1-year TULIP-1 and TULIP-2 trials, showed numerically greater improvements in SF-36 bodily pain and mental health domains compared with placebo, although the estimated between-group difference did not achieve statistical significance (65).

In the PAISLEY study, deucravacitinib treatment showed greater improvements in pain and fatigue at week 48 than placebo. Moreover, clinically meaningful responses in HRQoL were reported by fewer patients receiving placebo than those receiving deucravacitinib at week 48 (66).

A *post-hoc* analysis of data from four phase III trials of belimumab in SLE demonstrated that, at week 52 from treatment initiation, patients in LLDAS, DORIS remission and sustained LLDAS or DORIS remission experienced statistically significant and clinically meaningful improvements in all HRQoL outcomes compared with baseline. However, notable frequencies of persistently impaired HRQoL were observed in all four patient subgroups (67).

In a longitudinal observational study on a Swedish SLE cohort with a median follow-up of 8.5 years, being in LLDAS and being sustainedly in LLDAS was coupled with favourable HRQoL, pain, fatigue and overall health experience, even with LLDAS exclusive of clinical remission. However, in this study antidepressant use at any time during follow-up appeared to be a strong determinant of poor PROs (68).

In a large Chinese cohort of 510 SLE patients, the SLE-DAS score correlated significantly with all the LupusPRO HRQoL item scores except cognition. Moreover, patients with SLE-DAS index-based remission reported a significantly higher LupusPRO HRQoL score compared to those without and the improvement in SLE-DAS score over 6 months was also associated with improvement in HRQoL (69).

Data from the literature confirm that the relationship between disease status and HRQoL in SLE is not straightforward and that clinically desirable states do not necessarily translate into acceptable patient-perceived health (65).

A study from an Italian cohort of SLE patients in stable remission demonstrated that a heterogeneity exists as far as HRQoL is concerned among individuals with well-controlled SLE. In fact, a cluster analysis starting from PROs results in this 'ideal' cohort of remitted patients identified two different clusters of patients: one characterised by a 'high symptom burden' (HSB), and one characterised by a 'low symptom burden' (LSB), in terms of fatigue, disease impact on daily living and physical and mental health. A comorbid fibromyalgia and ongoing glucocorticoid treatment emerged as independent predictors of belonging to the HSB cluster. Importantly, patients in the HSB cluster presented higher SLAQ scores compared with those in the LSB cluster, indicating that a poorer HRQoL is accompanied by a tendency to overestimate disease activity by the patients (70).

Growing evidence in the literature demonstrates that PROs not only provide insights into patients' perspective, but they are also associated with short- and long-term disease outcomes. Nose *et al*. (71) examined the association between the LupusPRO score at baseline and longitudinal SDI scores among 1295 patients of the LUNA registry (the Lupus Registry of Nationwide Institutions) in Japan. Patients with higher HRQoL of LupusPRO at baseline demonstrated a significantly lower increase in SDI (71).

Recent data from the Almenara Lupus Cohort show that damage accrual is also associated with 'self-efficacy', a concept that implies the perceived capacity of working in partnership with health professionals to manage the diseases and related treatments. On a total of 209 patients and 563 visits, in the multivariable models, a better self-efficacy for managing symptoms and daily activities was predictive of less damage accrual and of a lower fatigue (72, 73).

Despite the increasing awareness of the importance of PROs to drive a more patient-centred approach, no specific core set of PROs has been defined and integrated into standard clinical evaluations. With the aim of bridging this gap, the LUPIN, a patient self-administered questionnaire, has been codesigned by patients and lupus experts under the leadership of the French national lupus patient association. As expected, the correlations between LUPIN components and physician's indices (SLEDAI, and PhGA) were statistically significant but weak. In contrast, a strong correlation was observed between the LUPIN global score and the SF-36 physical and pain domains (74).

Take-home messages

- According to data from RCTs, belimumab, anifrolumab and deucravacitinib show promising results in improving HRQoL (65-67).
- The relationship between disease status and HRQoL remains heterogeneous: even in well-controlled SLE,

a 'high symptom burden' phenotype persists and is strongly associated with fibromyalgia (70).

- PROs may be associated to short- and long-term disease outcomes: a worse HRQoL seems to be predictive of damage accrual, particularly in patients with low disease activity (71).
- The LUPIN questionnaire has been developed to capture symptoms that are often under-represented in conventional clinical indices and may support patient engagement and shared decision-making (74).

Conclusions

The literature published during 2025 further contributed to refining the understanding of SLE, highlighting both progress and persistent challenges across multiple domains. Advances in pathogenetic insights and biomarker research continued to support a more precise characterisation of disease activity, organ involvement and outcomes, while clinical and real-world studies provided additional evidence on treatment strategies and long-term disease management.

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