Review

Systemic lupus erythematosus: one year in review 2025

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ABSTRACT

This review highlights key advancements in systemic lupus erythematosus (SLE) research during 2024, covering pathogenesis, novel therapies, biomarkers, and clinical outcomes. Notable findings include new insights into immune dysregulation, promising therapeutic targets, and real-world data confirming the efficacy of anifrolumab and belimumab. Advances in biomarkers enhance disease monitoring, while multidisciplinary approaches improve reproductive outcomes and quality of life. These developments contribute to refining SLE treatment strategies and patient management.

Introduction

This review highlights the most significant advancements in systemic lupus erythematosus (SLE) research that emerged in 2024, continuing the tradition of the annual *One Year in Review* series (1). SLE is a chronic autoimmune disease characterised by a complex and partially elucidated pathogenesis, leading to a wide range of clinical and serological manifestations. A comprehensive MEDLINE search was conducted for studies published between January 1 and December 31, 2024, using MESH terms and keywords related to pathogenesis and new targeted therapies, biomarkers, clinical aspects and outcomes (included patient-reported outcomes), comorbidities, reproductive health, gender-related issues, phase I-IV clinical trials and real word evidence. The most relevant articles were selected, excluding reviews and case reports. The aim of this review is to offer a valuable summary of the latest advancements in SLE research.

Advances in pathogenesis and targeted therapies

In 2024, significant research advancements have provided deeper insights into the pathogenesis of SLE, with the goal of identifying novel therapeutic targets.

It is well established that platelets and neutrophil extracellular traps (NETs) play a crucial role in SLE-associated inflammation, immune dysregulation, and cardiovascular risk. Tay *et al*. investigated the role of low-density neutrophils (LDNs) and platelet-expressed Toll-like receptor 7 (TLR7) in the pathogenesis of SLE and lupus nephritis (LN). Through flow cytometry analysis of blood samples from 290 SLE patients and healthy controls, as well as experiments on TLR7-deficient mice, they identified a clinical correlation between LDNs, the neutrophil-to-platelet ratio (NPR), and disease activity. Patients with active disease exhibited higher levels of LDNs, which were more immature in those with kidney dysfunction. LDNs play a pivotal role in immunopathogenesis by preferentially binding to platelets, forming platelet-neutrophil complexes (PNCs) and promoting NETosis, exacerbating inflammation and tissue damage in SLE. Notably, PNC formation is dependent on platelet TLR7 expression. In TLR7-deficient mice, platelet-neutrophil binding and NETosis were significantly reduced. Furthermore, platelet-neutrophil interactions, mediated by platelet TLR7, were associated with increased neutrophil infiltration in SLE-affected renal tissue. These findings suggest that NPR could serve as a predictive biomarker for lupus nephritis flares, while TLR7-dependent platelet-neutrophil crosstalk may represent a promising therapeutic target for LN (2).

The role of interferon (IFN) in SLE pathogenesis is well recognised. Through metabolomic and proteomic analyses of monocytes from SLE patients and healthy volunteers, Montano *et al*. demonstrated that IFN-α induces

persistent epigenetic changes in SLE monocytes, contributing to chronic activation and inflammation. Their findings indicated that SLE monocytes exhibit increased glycolysis and oxidative phosphorylation (OXPHOS) and elevated levels of isocitrate dehydrogenase 2 (IDH2), an enzyme that converts isocitrate to α-ketoglutarate (α-KG), a cofactor for histone demethylases. These metabolic alterations regulate interferon-stimulated gene (ISG) activation through KDM6A/B demethylases. This link between metabolic and epigenetic reprogramming mediated by IFN-α presents a potential therapeutic target (3).

SLE is characterised by aberrant activation of proinflammatory T cells and impaired regulatory T cells (Treg) function. Roach *et al*. explored the relationship between Pbx1 (Pre-B cell leukaemia homeobox 1) and STAT3 in Treg in lupus using murine models. Overexpression of the dominant-negative Pbx1-D or Pbx1 deletion altered STAT3 activity, affecting T cell differentiation, cell cycle regulation, and apoptosis. These findings suggest that dysregulation of the PBX1/STAT3 axis may contribute to SLE pathogenesis by modulating immune responses (4).

It is known that oxidative stress (OS) is involved in the pathogenesis of SLE; to explore this, Chen *et al*. analysed long non-coding RNAs, microRNAs, and messenger RNAs: 42 differentially expressed mRNAs (DEmRNAs) were identified, with enrichment in neutrophil-related biological processes. The XIST/FOS and XIST/MME axes were identified as potential OS-related regulatory pathways in SLE (5). The findings provide insights into immune dysregulation and oxidative stress mechanisms, offering potential targets for therapeutic intervention.

While the role of IgG autoantibodies in SLE pathogenesis have been extensively studied, the role of IgA remains underexplored. Waterman *et al*. investigated the contribution of IgA1 autoantibodies to plasmacytoid dendritic cells (pDC) activation and IFN production in SLE. IgA1 autoantibodies enhance pDC activation and IFN production, as pDCs express both FcαR (CD89) (the IgA-specific receptor) and FcγRIIa (CD32a) (the IgG receptor), IgA1 autoantibodies synergise with IgG in Sm/RNP ICs, inducing a more robust type I IFN response in pDCs. These findings highlight a previously unrecognised role of IgA1 autoantibodies in amplifying pDC-driven IFN responses, suggesting that targeting FcαR may provide a novel therapeutic strategy to mitigate IFN-driven inflammation in SLE (6).

Progress has not only been made in elucidating SLE pathogenesis but also in the development of new targeted therapies.

Lysophosphatidic acid (LPA) shows promise as a new treatment for SLE-related glomerulonephritis by reducing macrophage activation, systemic inflammation, and immune complex-mediated damage in experimental models. It effectively lowers anti-dsDNA antibody levels and key cytokines (TNF-α, IL-6, IL-18) while reducing glomerular IgG deposition and urinary albumin levels. Unlike stronger immunosuppressants, LPA does not cause excessive immune suppression, though its long-term risks require further study (7).

SLE is driven by excessive type I IFN production from pDCs. Blood dendritic cell antigen 2 (BDCA2) is a receptor exclusively expressed on pDCs, and its activation via monoclonal antibodies suppresses IFN-I production. A BDCA2 antibody-drug conjugate (BDCA2-ADC) was developed by conjugating a glucocorticoid receptor agonist to BIIB059 to enhance therapeutic efficacy. BDCA2-ADC operates via a dual mechanism: it suppresses IFN-I production through BDCA2 blockade, while delivering targeted glucocorticoid therapy to pDCs. Compared to BIIB059, BDCA2-ADC demonstrates superior cytokine inhibition, enhanced immune regulation, and potentially improved clinical efficacy, marking it as a promising therapy for SLE (8).

PF-06835375 is a novel CXCR5-targeting antibody designed to deplete B cells, follicular helper T cells (Tfh), and circulating Tfh-like cells, which are integral to autoimmune processes. A phase 1, randomised, double-blind, placebo-controlled, first-in-human study evaluated PF-06835375 in patients with SLE and rheumatoid arthritis, as well as its effects on vaccine response. PF-06835375 was well tolerated and demonstrated robust, sustained depletion of B and Tfh cells. Notably, the drug preserved responses to tetanus/diphtheria and meningococcal B vaccines, suggesting a distinct mechanism relative to other B-cell-targeting therapies. These results support the further clinical development of PF-06835375 as a potential treatment for autoimmune diseases (9).

Povetacicept (ALPN-303) is a novel Fc-fusion protein that potently inhibits both BAFF and APRIL, offering greater efficacy than existing BAFF/APRIL-targeting therapies. A phase 1, randomised, double-blind, placebo-controlled study showed that povetacicept was well tolerated across all doses, and resulted in reductions in free BAFF and APRIL levels, naive B cells, and antibody-secreting cells. These findings support further clinical development of povetacicept in autoimmune diseases such as IgA nephropathy, lupus nephritis, and autoimmune haemolytic anaemia (10).

These recent advancements provide promising avenues for improving the understanding and treatment of SLE, with novel therapeutic targets and approaches aimed at mitigating disease progression and associated complications.

Take home messages

- Low-density neutrophils (LDNs) and platelet-expressed Toll-like receptor 7 (TLR7) play key roles in SLE pathogenesis, particularly in lupus nephritis (LN), through NETosis activation (2). Another potential driver of pathogenesis may be the PBX1/STAT3 axis (4) and XIST/FOS axes (5).
- The pivotal role of interferon (IFN) in SLE pathogenesis is well established. The epigenetic changes mediated by IFN, as well as the role of dendritic cells and IgA in its production, are currently being investigated as potential therapeutic targets (3, 6, 8).
- New target treatments seem to have great potential: LPA (7), PF-06835375 targeting CXCR5 (9) and Povetacicept that inhibits BAFF/APRIL more effectively than existing therapies (10).

Biomarkers

Currently, no single surrogate biomarker exists to make diagnosis or to predict disease outcomes, largely due to the heterogeneity of the disease. Recent research has identified several promising biomarkers for infection risk, cardiovascular disease, and disease progression in SLE.

A subset of these studies specifically explores biomarkers for predicting relapses, histologic features, and treatment response in LN, one of the most severe SLE manifestations. Using large-scale single-cell RNA sequencing and single-cell T-cell receptor sequencing on renal biopsy tissues, Chen *et al*. identified a rare dendritic cell population (DC3) that was highly activated in LN kidneys and exhibited a strong proinflammatory phenotype. The abundance of DC3 cells in the kidney correlated with LN progression and poor prognosis, suggesting that quantifying kidney DC3 cells could serve as a predictive biomarker for induction treatment response in LN patients (11).

An ancillary study of the prospective WIN-Lupus clinical trial suggests that IgE anti-dsDNA antibodies could serve as a non-invasive predictive biomarker for LN relapse risk after 2–3 years of maintenance therapy, particularly in patients discontinuing maintenance immunosuppressive therapy, providing valuable insights for personalised treatment management (12).

In a separate study, Fava *et al*. analysed peripheral blood samples from 279 SLE patients with proteinuria who underwent kidney biopsies. Their findings indicate that anti-C1q and anti-dsDNA antibody levels are significantly higher in proliferative LN compared to non-proliferative forms. Moreover, patients with proliferative LN who achieved a complete treatment response had higher baseline levels of these antibodies than those with partial or no response. These results suggest that baseline anti-C1q and anti-dsDNA levels may serve as non-invasive biomarkers for proliferative LN, with anti-C1q potentially predicting complete treatment response at the time of kidney biopsy (13).

Elevated serum uric acid (SUA) levels are associated with cardiovascular and kidney disease and are an independent predictor of renal arteriolar damage and poor prognosis in LN patients. Hyperuricaemia is a strong risk factor for progression to end-stage renal disease or death. LN patients with hyperuricemia had higher blood pressure, hyperlipidaemia, lower eGFR, lower haemoglobin, lower serum albumin, and more severe renal damage compared to those with normal SUA levels. Additionally, high SUA levels were significantly associated with increased lupus nephritis severity, renal arteriolar damage, and proteinuria (14).

Another potential biomarker under investigation is red blood cell distribution width (RDW), a measure of variability in red blood cell size that has been associated with inflammatory and autoimmune diseases. In a study by J. Mercader-Salvans *et al*., RDW was found to be significantly higher in SLE patients than in healthy controls (p=0.003). Moreover, elevated RDW levels were associated with urinary abnormalities (such as haematuria and urinary casts), low complement levels (a marker of disease activity), fever, mucosal ulcers, and cardiovascular complications (including angina, pulmonary hypertension, and venous thrombosis) (15).

Inflammatory pathways may play a crucial role in cardiovascular complications in SLE. A study by Olivera *et al*. assessed vascular function and found increased arterial stiffness, vascular inflammation, and a higher burden of non-calcified coronary plaques compared to healthy controls. These vascular abnormalities were associated with elevated circulating cytokines and chemokines (including IL-12B, CXCL9, MCP-4, CXCL6, and CCL23), suggesting a potential link between inflammation and accelerated cardiovascular disease progression (16).

Beyond cardiovascular involvement, researchers have also explored shared pathogenic mechanisms between SLE and other autoimmune diseases. A bioinformatics analysis identified similarities between SLE and inflammatory bowel disease (IBD). Five key genes (KLRB1, KLRF1, GZMK, IL7R, and CD40LG) were proposed as diagnostic markers, while both diseases exhibited similar immune cell infiltration patterns, pointing to potential overlapping therapeutic strategies (17).

Conversely, WNT16, a member of the WNT protein family, has been proposed as a biomarker that may help distinguish SLE from other autoimmune diseases. A study involving 162 SLE patients found that WNT16 expression was significantly reduced in SLE, correlating with disease activity, clinical manifestations, and specific laboratory markers. Additionally, WNT16 may contribute to SLE pathogenesis by regulating cell proliferation and apoptosis, opening new avenues for targeted therapeutic approaches (18).

Emerging research has also focused on B-cell dysregulation in SLE. Patients with active disease had higher CD19+ Siglec-10+ B cells expression on naive B cells compared to inactive SLE patients and healthy controls. These cells exhibit increased CD40 and reduced CD21, both markers of immune activation. Interestingly, the proportion of Siglec-10+ naive B cells correlate with disease severity (as measured by the SLEDAI-2K score). This finding highlights the potential role of Siglec-10+ naive B cells as a biomarker for disease progression and a tool for monitoring immune dysregulation in SLE (19).

It is crucial to predict infection risk among SLE patients, it seems that individuals with higher levels of CD8+ CD38+ T-cell experienced more frequent recurrent infections, suggesting that this easily measurable biomarker could help identify high-risk patients and guide preventive clinical interventions (20).

Finally, researchers have begun exploring biomarkers for neuropsychiatric SLE (NPSLE), particularly in peripheral nervous system involvement. While several serum and cerebrospinal fluid (CSF) biomarkers have been associated with central NPSLE manifestations, research on peripheral NPSLE remains limited. A multicentre international SLE inception cohort identified anti-KIF20B antibodies as a potential biomarker for SLE-related cranial neuropathies, a rare but debilitating NPSLE manifestation (21).

Take home messages

- Lupus nephritis (LN) severity and treatment response may be predicted using novel biomarkers, including DC3 dendritic cells, anti-dsDNA IgE, anti-C1q, and serum uric acid levels, which correlate with disease progression and relapse risk (11-14), also RDW may serve as a surrogate indicator of disease activity and cumulative damage in SLE (15).
- Inflammatory pathways and immune cell markers such as CD8+ CD38+ T cells, Siglec-10+ naive B cells, and cytokine profiles play a crucial role in cardiovascular risk, disease severity, and immune dysregulation in SLE, offering potential for personalised therapeutic strategies (16, 20).
- Emerging connections between SLE and other autoimmune diseases, including inflammatory bowel disease (IBD), WNT16-related pathways, and neuropsychiatric lupus biomarkers (anti-KIF20B antibodies), highlight shared mechanisms and new avenues for targeted treatments (17, 18, 21).

Clinical aspects and outcomes

The complexity and chronic nature of SLE highlight the importance of identifying predictors of long-term outcomes. Notably, achieving sustained remission (DORIS) or maintaining low disease activity (LLDAS) significantly reduces the risk of organ damage and disease flares, with longer durations offering greater protection against severe complications (22). Currently, particular attention is being given to disease activity and glucocorticoid use as key predictors of organ damage and mortality (23).

Further research has focused on treatment response in lupus nephritis (LN). A lower chronicity index and the presence of anti-dsDNA antibodies appear to be associated with a higher likelihood of a sustained response. This was demonstrated in a study by Izmirly *et al*., which analysed response rates and predictors of treatment success in 180 patients with class III, IV, and/or V LN and a baseline urine protein/creatinine (UPCR) ratio ≥1.0 (24).

Additionally, a complete renal response in lupus nephritis is associated with significantly better long-term kidney survival, reinforcing the need for aggressive disease management to prevent progression to end-stage kidney disease (25) .

In the field of NPSLE, Palazzo *et al*. identified male sex, a history of NP-SLE, and pre-existing neuropsychiatric damage as strong predictors of impending flares in patients receiving standard therapy with belimumab or placebo (26). Notably, patients with NP manifestations attributed to SLE had a significantly higher likelihood of clinical response when treated with immunosuppressants, highlighting their key role in NPSLE management (27).

Beyond neuropsychiatric manifestations, the long-term course and activity of SLE significantly impact health-related quality of life (HRQoL) (28). Achieving remission or low disease activity is associated with meaningful improvements in HRQoL, as measured by LupusPRO and SF-36, whereas fibromyalgia, organ damage, age, and glucocorticoid use contribute to worse outcomes (29). A retrospective analysis further revealed that patients with prolonged quiescent disease had better physical HRQoL and fewer depressive symptoms than those with chronic active or relapsing-remitting disease. However, even well-controlled patients continued to face challenges related to mental health, social functioning, and fatigue, emphasising the need for comprehensive management (28).

Fatigue, a hallmark symptom of both SLE and fibromyalgia, is strongly linked to reduced physical activity, pain, and sleep disturbances (30). Recent studies suggest that low-intensity treadmill and aerobic exercise can alleviate fatigue, and transcranial direct current stimulation combined with aerobic exercise (tDCS-AE) provides sustained benefits for up to 60 days. This highlights tDCS-AE as a safe, effective, and long-lasting non-pharmacological strategy for managing chronic fatigue in SLE (31).

Given these findings, developing multidisciplinary and non-pharmacological treatment approaches is crucial for improving patient outcomes and quality of life.

SLE is typically diagnosed in young adults, but data on very late-onset SLE (vlSLE, ≥60 years) remain limited. A study by Viveiros *et al*. found that compared to younger-onset SLE, vlSLE presented with lower rates of arthritis, renal involvement, and anti-dsDNA positivity, with no neuropsychiatric manifestations. Patients with vlSLE also exhibited lower C3 levels and anti-Ro positivity but had a poorer prognosis due to comorbidities. These findings highlight the importance of considering SLE in elderly patients with autoimmune symptoms (32).

Take home messages

- Achieving sustained remission (DORIS) or low disease activity (LLDAS) significantly reduces organ damage and flares in SLE, while disease activity and glucocorticoid use are key predictors of organ damage and mortality (22, 23).
- A complete renal response in lupus nephritis improves long-term kidney survival, emphasising the need for aggressive treatment. In neuropsychiatric SLE, male sex, previous NPSLE episodes, and pre-existing neuropsychiatric damage predict future flares, with immunosuppressive therapy improving clinical outcomes (24-27).
- Disease activity levels and organ damage significantly affect HRQoL. Fatigue, a major contributor to poor quality of life, can be effectively managed with non-pharmacological strategies such as transcranial direct current stimulation combined with aerobic exercise (tDCS-AE) (28, 30-32).

Comorbidities and organ damage

The treatment landscape for SLE is rapidly evolving with the introduction of new biologic and non-biologic therapies. Optimising comorbidity management, particularly addressing cardiovascular and infectious risks, is crucial to preventing long-term organ damage.

Cardiovascular risk assessment and mitigation have become key priorities in SLE care; however, adherence to recommended guidelines remains suboptimal in real-world practice. A recent multicentre cross-sectional study of over 3,400 SLE patients across five

continents highlighted poor control of cardiovascular risk factors. While target attainment rates for BMI and blood pressure were low, smoking cessation was achieved in up to 88% of cases. Risk control was especially inadequate in patients with antiphospholipid syndrome (APS) and in middle-income countries (33).

A 10-year vascular ultrasound follow-up study of 111 SLE patients and 94 controls confirmed an increased risk of carotid plaque progression in SLE. However, sustained cardiovascular risk factor control and prolonged remission (≥75% of follow-up in DORIS-defined remission) were associated with slower plaque progression, though their impact on long-term cardiovascular events remains uncertain (34).

Beyond traditional risk factors, SLE-related atherosclerosis may involve distinct pathogenic mechanisms. A cross-sectional NMR metabolomics study in 164 SLE patients and 123 controls identified glycoprotein acetyls (GlycA) as biomarkers linked to dyslipidaemia, obesity, and myocardial infarction mortality, independent of disease activity. Additionally, glycolysis metabolites were associated with diabetes risk, suggesting that metabolomic profiling could improve cardiovascular risk stratification in SLE (35).

Certain medications influence the risk of comorbidities, particularly CV events (CVEs) and infections. A case-control study of over 52,000 SLE patients found that current hydroxychloroquine use significantly reduced CVE risk, including myocardial infarction (adjusted OR 0.63, 95% CI 0.57–0.69), while past use provided no protection, supporting the need for continuous therapy (36).

Conversely, a meta-analysis of LN induction therapy of randomised controlled trials showed a dose-dependent link between glucocorticoids and serious infections, with a threefold higher risk in patients on 60 mg/day of prednisone equivalents compared to 25 mg/day (37). While high-dose GCs improve renal response rates, treatment should be tailored to individual risk profiles, particularly in frail patients who face increased hospital readmission rates, mainly for sepsis (38).

As discussed above, maintaining stable low disease activity is crucial in moderate-to-severe SLE. However, the long-term impact of serologically active, clinically quiescent (SACQ) disease – characterised by anti-dsDNA positivity and/or hypocomplementaemia without clinical manifestations – remains unclear and is typically managed without treatment adjustments. A multicentre prospective study using unsupervised cluster analysis identified three SACQ subgroups: (1) patients with major organ involvement and higher onset age, associated with increased flare and damage risk; (2) those with milder disease and lower damage risk; and (3) patients with renal involvement and intermediate risk. These findings underscore the need for personalised monitoring strategies in SACQ SLE (35).

Take home messages

- CV risk factor control in SLE patients remains suboptimal, especially in patients with antiphospholipid syndrome (APS) and in middle-income countries. Sustained risk factor control and prolonged remission may help reduce carotid plaque progression (33, 34).
- Hydroxychloroquine reduces CV event risk, reinforcing the need for continuous use, while high-dose glucocorticoids increase serious infection risks, particularly in frail patients. Personalised treatment strategies are essential (36-38).
- Personalised monitoring is needed for SACQ SLE. Different SACQ subgroups have varying risks of disease progression and damage, underscoring the need for tailored follow-up and management strategies (35).

Reproductive health and gender-related issues

SLE predominantly affects females, making sex-related differences a key factor in disease manifestations and outcomes, particularly during pregnancy.

A retrospective cohort study of 1,048 biopsy-confirmed LN patients analysed sex-specific risk factors, including mortality. Male patients exhibited more aggressive disease features, such as earlier onset, higher blood pressure, increased serum creatinine, and more severe histopathological alterations, including a higher activity index. The overall mortality rate was significantly higher in males (24.2%) compared to females (13.4%). Notably, infections were the leading cause of death, disproportionately affecting male patients (39).

Pregnant women with SLE exhibit a Th1-dominant immune response, marked by elevated IFN-γ and reduced Th2 polarisation, which may contribute to pregnancy complications. Zhang *et al*. found significantly higher IFN-γ ($p<0.001$) and lower GATA3 ($p<0.01$) in pregnant SLE patients, leading to an increased Th1/Th2 ratio ($p<0.05$). This imbalance persisted throughout pregnancy and may be linked to preterm birth, intrauterine growth restriction, and preeclampsia. These findings underscore the role of immune dysregulation in SLE pregnancies, emphasising the need for targeted monitoring and interventions (40).

Placental abnormalities, including smaller placentas, infarctions, and increased perivillous fibrin deposition (PVFD), were significantly more common in SLE pregnancies with small-for-gestational-age (SGA) infants. Notably, all placentas exhibiting PVFD were associated with SGA births. Compared to non-SLE pregnancies with SGA, PVFD was more prevalent in SLE, suggesting a distinct mechanism of placental injury in these patients (41).

Preeclampsia is another adverse pregnancy outcome (APO) reported more frequently in SLE. Rector *et al*. investigated whether early HCQ use could reduce preeclampsia risk in SLE pregnancies. Although HCQ-exposed patients had higher comorbidities, no significant association was found between HCQ and preeclampsia. Further research is needed to determine the potential role of HCQ in mitigating preeclampsia risk in high-risk SLE pregnancies (42).

The long-term health of infants born to mothers with SLE remains an area of ongoing investigation. Gernaat *et al*. tried to investigate the infection risk in the first year of life in infants born to mothers with SLE. They had a higher incidence of infections within the first year of life compared to infants from

the general population. Preterm birth accounted for 86% of the increased infection risk in the first 72 hours and 27% over the first year, highlighting prematurity as a key contributor to neonatal susceptibility (43) .

Furthermore, female SLE patients face additional challenges related to pregnancy. The P-RHEUM.it study recently collected real-world data on pregnancy outcomes in Italy from 2018 to 2023. Disease flares occurred in 16.6% of SLE pregnancies, while complications were reported in 37.9% of cases. However, multidisciplinary preconception counselling, close monitoring, and individualised risk stratification were associated with generally favourable pregnancy outcomes (44). For SLE patients, contraception is essential to prevent unplanned pregnancies and mitigate risks associated with active disease or teratogenic medications. Clowse *et al*. analysed data from the RISE registry, which collects observational data from rheumatology practices in the USA. Between 2019 and 2021, contraception documentation rates remained low. Higher documentation rates were associated with factors such as younger age, more frequent visits, female providers and certain regions. Surprisingly, teratogenic medication use did not influence contraception documentation (45).

Therapy adherence remains a critical issue for SLE patients, also during pregnancy. A recent study of 200 patients (50% pregnant) revealed that approximately 30% had inadequate adherence to prescribed rheumatic disease medications. Anxiety was identified as a contributing factor to poor adherence. Interestingly, pregnant patients exhibited better adherence, likely due to dedicated preconception counselling and close monitoring programmes (46).

Take home messages

- Pregnant women with SLE show a persistent Th1-dominant immune response, which may contribute to complications such as preterm birth and preeclampsia, highlighting the need for targeted monitoring and interventions (40).
- Male SLE patients exhibit more severe disease features and higher mortality rates, primarily due to infections. This underscores the need for tailored management strategies in male SLE patients (39).
- Dedicated pre-conception counselling and close monitoring during pregnancy may improve adherence to treatment and lead to favourable pregnancy outcomes in women with SLE. This highlights the importance of multidisciplinary care to mitigate disease impact on maternal and foetal health. (46).

Treatment: clinical trials and drug discovery

In recent years, the therapeutic landscape for systemic lupus erythematosus has expanded with newly approved treatments, while many emerging therapies remain under investigation.

Among these, Janus kinase (JAK) inhibitors have shown promise and are already approved for conditions such as rheumatoid arthritis and psoriatic arthritis.

A recent 48-week phase II randomised, double-blind, placebo-controlled trial evaluated upadacitinib, a selective JAK1 inhibitor, alone or in combination with elsubrutinib, a Bruton tyrosine kinase (BTK) inhibitor, in adults with moderate-to-severe SLE. Both the upadacitinib monotherapy (30 mg QD) and the combination therapy (ABBV-599 high dose: upadacitinib 30 mg + elsubrutinib 60 mg QD) met the primary endpoint (SRI-4 response with glucocorticoid dose ≤10 mg/day) and multiple secondary endpoints, demonstrating potential to reduce disease activity, flare frequency, and time to first flare compared to placebo (47).

Another promising approach involves E6742, a TLR7/8 inhibitor that modulates type I IFN and inflammatory cytokine production. In a phase I/II study in Japan, patients received E6742 (100 mg or 200 mg BID) or placebo for 12 weeks. The treatment showed an acceptable safety profile, a ~90% reduction in the interferon signature within two weeks, and improvements in BICLA response (placebo: 33.3%; 100 mg: 37.5%; 200 mg: 57.1%), CLASI-50 score, joint counts, and anti-dsDNA levels (48).

Given the role of interferon in SLE pathogenesis, particularly in skin manifestations, Burge *et al*. explored RSLV-132, an RNase-IgG1 fusion protein designed to degrade extracellular RNA, thereby reducing type I interferon production and pro-inflammatory cytokines (IL-6, TNF-α). A phase II trial in 65 patients with moderate-to-severe skin disease (CLASI ≥10) and RNA-binding autoantibody positivity showed no significant improvement in mean CLASI score *versus* placebo, but better responses in subgroups with higher baseline CLASI and SLEDAI scores. RSLV-132 could be potentially less toxic than traditional immunosuppressive therapies (49).

In addition to developing new therapies, efforts have also focused on optimising the use of established treatments for SLE. Mycophenolate mofetil (MMF) has been the subject of two recent studies evaluating its efficacy in newly diagnosed disease and the impact of its discontinuation in patients in sustained remission.

The first study, by You *et al*., assessed MMF combined with prednisone and hydroxychloroquine in newly diagnosed SLE patients without major organ involvement. Compared to a control group receiving only steroids and immunomodulators, early MMF treatment significantly reduced severe flares and the incidence of lupus nephritis, suggesting a protective role in preventing disease progression (50).

The second study, by Chakravarty *et al*., examined MMF discontinuation in patients with stable disease control for at least two years (renal indication) or one year (other indications). Over 60 weeks, the risk of disease reactivation was 11% in the maintenance group *versus* 18% in the withdrawal group, with a higher relapse rate in those with prior renal involvement (51).

Post-hoc analyses of existing SLE treatments have also provided valuable insights. A pooled analysis of four phase III belimumab trials (BLISS-52, BLISS-76, BLISS-SC, BLISS-Northeast) by Gómez *et al*. evaluated different dosages and administration routes in preventing renal flares in active SLE patients without severe nephritis. Intra-

venous belimumab reduced renal flare risk at both low (1 mg/kg: -58%) and high (10 mg/kg: -38%) doses, while the subcutaneous route showed no significant effect. The combination of belimumab with antimalarials further decreased renal flare risk (HR 0.66), with the lowest flare rates observed in patients receiving IV belimumab (1 mg/kg) plus antimalarials (51).

Further evidence comes from a *post-hoc* analysis by Rovin *et al*. of the NOBILITY trial, which assessed the anti-CD20 monoclonal antibody Obinutuzumab in 125 patients with active proliferative lupus nephritis (ISN/RPS class III/IV). Extended follow-up confirmed superior renal outcomes with obinutuzumab plus standard of care (SOC), including lower proteinuria, reduced renal flare risk (HR 0.57), higher complete renal response rates, and decreased glucocorticoid use. More patients in the obinutuzumab group maintained remission on prednisone doses below 7.5 mg/day (52).

Take home messages

- The SLE treatment landscape is evolving with promising new drugs, including JAK inhibitors like upadacitinib and BTK inhibitors such as elsubrutinib, which have shown efficacy in reducing disease activity and flares (47).
- Novel approaches, such as the TLR 7/8 inhibitor E6742 (48) and the RNase-IgG1 fusion protein RSLV-132, aim to modulate type I interferon activity, a key driver of SLE pathology, particularly in skin and systemic manifestations (49).
- Studies on mycophenolate mofetil (MMF) highlighted its benefits in early disease control (50) and the risks associated with its discontinuation, particularly in patients with prior renal involvement (53).
- *Post-hoc* analyses on belimumab highlight its role in lowering renal flare risk, especially when combined with antimalarials (51); obinutuzumab also shows promise for improving renal outcomes in lupus nephritis (52).

Treatment: real world evidence

Although published data remain limited just a few years after the drug was approved, observational studies are systematically gathering real-world clinical data on anifrolumab. One such study, the ongoing multinational Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER), recently published its protocol. It outlines a three-year follow-up period starting from the first drug infusion (54).

Among the first real-world insights, an Italian multicentre study confirmed the rapid efficacy of anifrolumab, with significant improvements in SLEDAI-2K, SLE-DAS, Physician Global Assessment, CLASI-activity, and joint count observed as early as four weeks. The safety profile was acceptable, and by six months, 50% of patients had achieved remission, while 80% had reached low disease activity (LLDAS) (55).

Belimumab seems to facilitate treatment goal attainment in real-world settings, showing improved disease control (based on SRI-4), LLDAS and DORIS remission achievement, a steroid-sparing effect, good tolerability with a low incidence of adverse events (56),

The glucocorticoid-sparing effect of belimumab was further supported by a retrospective real-world study. The BESST study documented a significant reduction in daily prednisone dosage at six months, which was maintained at 12 and 24 months (57).

Starting belimumab before immunosuppressants led to better health outcomes, including earlier glucocorticoid tapering, fewer disease flares, and delayed onset of new organ damage compared to patients who received belimumab after immunosuppressants (58). It was confirmed by a study of Tani *et al*. that highlighted a shift in belimumab prescription trends with increasing use in immunosuppressant-naive patients. While LLDAS5 and remission rates were similar between IS-naive and previously treated patients, the IS-naive group required significantly lower GC doses at six and 12 months (59).

Data from the LOOPS registry suggest that adding belimumab to the standard of care (SoC) improves the management of proliferative LN. In patients with biopsy-proven class III or IV LN, the belimumab+SoC group showed higher complete renal response (CRR) rates at 52 weeks, alongside lower glucocorticoid doses, lower SLICC Damage Index scores, and fewer adverse events. Notably early belimumab initiation was associated with CRR achievement in treatment-resistant cases (60).

A Chinese monocentric study found that belimumab and telitacicept (BAFF/APRIL inhibitors) facilitated early LLDAS achievement by week 24. Risk factors for LLDAS failure included low baseline lymphocyte count, low serum albumin levels, and haematological involvement (61).

These findings were supported by a multicentre study, which reported higher SRI-4 response rates at 24 weeks in patients treated with telitacicept compared to belimumab, although this difference disappeared by week 52 (62). Additionally, in 30 LN patients, the addition of telitacicept to SoC reduced disease activity and daily GC doses, with a favorable safety profile (63).

While available data suggest that LLDAS and remission are realistic treatment goals in clinical practice, the optimal timing for therapy adjustment when targets are not met remains unclear, particularly in non-renal SLE. A monocentric cohort study of 81 patients with extrarenal flares identified six months as a critical time point for assessing treatment response in a T2T approach. The majority of patients achieved LLDAS5 in six months, with very few late responders. Notably, immunosuppressant adjustments at six months were significantly associated with higher LLDAS5 and remission rates at 12 months (64).

Take home messages

- Real-world evidence supports the effectiveness of anifrolumab in SLE treatment, demonstrating rapid disease control, a steroid-sparing effect, and a favourable safety profile (55).
- Belimumab provides sustained benefits in real-world settings, promoting LLDAS and remission while reducing glucocorticoid dependence (56, 57). Early initiation, particularly in LN and IS-naive patients, is associated with better disease control and improved long-term outcomes (58-60).

- In a T2T approach, the six-month assessment period is a critical time point for evaluating treatment response, as late responders beyond this window are rare, and early immunosuppressant adjustments significantly enhance remission rates (64).

Conclusion

Over the past year, numerous significant studies on systemic lupus erythematosus (SLE) have been published, reflecting the growing interest in this complex disease. In this review, we have selected and summarised the most relevant findings, covering various aspects. In line with the *One Year in Review* collection, we have particularly focused on the potential implications of these insights in clinical practice. While these advancements have contributed to a better understanding of SLE, further research is essential to deepen our knowledge and improve patient care.

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