One year in review

Systemic lupus erythematosus: one year in review 2023

D. Zucchi[1,2], E. Silvagni[3], E. Elefante[1], V. Signorini[1], C. Cardelli[1,2], F. Trentin[1], D. Schilirò[1], G. Cascarano[1], A. Valevich[1], A. Bortoluzzi[3], C. Tani[1]

[1]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;*
[2]*Department of Medical Biotechnologies, University of Siena;*
[3]*Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria S. Anna, Ferrara, Italy.*

Dina Zucchi, MD
Ettore Silvagni, MD, PhD
Elena Elefante, MD
Viola Signorini, MD
Chiara Cardelli, MD
Francesca Trentin, MD
Davide Schilirò, MD
Giancarlo Cascarano,
Anastasiya Valevich,
Alessandra Bortoluzzi, MD, PhD
Chiara Tani, MD, PhD

Please address correspondence to:
Dina Zucchi
U.O. di Reumatologia,
Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: dinazucchi@hotmail.it

Received on February 27, 2023; accepted in revised form on March 13, 2023.

Clin Exp Rheumatol 2023; 41: 997-1008.

Key words: systemic lupus erythematosus, pathogenesis, clinical manifestations, treatment

Competing interests: none declared.

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide range of clinical manifestations and a relapsing-remitting course.

New data regarding pathogenic pathways, biomarkers and clinical manifestations of SLE are emerging, and new drugs and therapeutic protocols have been proposed to improve the control of disease activity. Furthermore, new insights into comorbidities and reproductive health in SLE patients are constantly emerging.

This annual review aims to summarise the most relevant data on SLE that was published in 2022.

Introduction

This *review* aims to describe the most relevant novelties regarding systemic lupus erythematosus (SLE) that emerged in 2022, in line with the previous annual One Year in Review of this series (1).

We performed a Medline search of English language articles published from the 1st January to 1st December 2022 using the following key words: "systemic lupus erythematosus" AND "pathogenesis", "biomarkers", "clinical manifestations", "comorbidities", "remission", "low disease activity", "patients-reported outcomes", "precision medicine", "COVID19", "infections", "therapy", "pregnancy" and related terms.

The most relevant original articles regarding adult SLE were selected for inclusion in this review, while case reports and review articles were excluded.

Pathogenesis

SLE expression is the result of both innate and adaptative immune system complex interactions, and genetic, epigenetic, and environmental factors contribute to it. During 2022 particular emphasis was given to the role of innate immunity in SLE, in the wake of recent acquisitions on type I interferon (IFN I) pathway.

Iwamoto *et al*. (2) explored the association between IFN I activity and lupus nephritis (LN) correlating serum IFN activity with the expression of IFN-induced genes and proteins in renal tissue cells. They found a higher proliferative LN prevalence in patients with high serum IFN, and in renal biopsies IFN-signature expression was mostly increased in the glomerular areas of active LN kidneys, suggesting a possible bloodstream source of IFN in the pathogenesis of LN.

Instead, Siddiqi *et al*. (3) provided new evidence on the association of IFN signature with disease activity. A cluster of infrequently investigated IFN-regulated genes (IRGs) (type II IRGs) with potential significance for SLE pathogenesis was analysed, and an association between this subset and disease activity was found, paving the way for the inclusion of other IRGs genes in future assessments of IFN signatures in SLE.

The analysis of the Illuminate trials data showed an association between anti-RNP antibodies and IFN gene signatures (IGS), suggesting that anti-RNP immune complexes may drive the IGS without complement fixation (4).

As for novel evidence on genetic factors in SLE pathogenesis, seven single nucleotide polymorphisms from IL-1β, IL-10, and TNF-α genes were found to affect the risk of SLE and some of them seem to be connected to the SLE phenotype (5). Moreover, a link between specific genotypes and the serum concentrations of TNF-α, IL-1β, and IL-10 was found.

New evidence on the overlap between genetics and epigenetics has been provided by Zhao *et al*. (6). The authors described an alteration of the 3D ge-

nome organisation in the CD4+ T cells of patients with SLE and its association with disease activity; interaction loops within chromosomes associated with SLE disease activity was analysed, revealing the potential relationship between transcription factors, histone modifications, genetic variation and differentially expressed genes in SLE.

Noteworthy insights came from another work (7) in which effects of immunosuppressant (IS) exposure on genetic expression in SLE has been analysed. This study explored a selection of disease-relevant gene "modules"– a tool increasingly used in genetic studies – in a large cohort of SLE patients. A marked impact of medication exposure, in particular glucocorticoids (GCs), on gene module expression was found, highlighting the need to take this variable into account in blood transcriptional profiling studies, to better interpret the results and avoid misleading data.

Take home messages

- Interferon signatures in SLE are complex and type II IFN-related genes appear to be preferentially upregulated in SLE patients with higher disease activity (3).
- Disease-specific medications, in particular glucocorticoids, have a significant effect on genetic expression in SLE patients, and therapy data from SLE cohorts should be taken into account in the study design of gene expression in SLE (7).

Biomarkers

Last year, several studies on this topic were published with new interesting findings.

In a study of 232 SLE patients, high levels of sialic acid binding Ig-like lectin 1 (SIGLEC1), an IFN-1 surrogate marker had highly (92.2%) negative diagnostic value, but less sensitive positive predictive value (72.8%), suggesting that it may help to exclude SLE in suspected cases (8).

Other biomarkers such as SIRT1 (sirtuin-1) and soluble ST2 correlated with disease activity (9, 10). Also, interleukin-6 was higher in the plasma of patients with active SLE in comparison with quiescent cases (11). The levels of a number of other biomarkers correlated with renal involvement, for instance, urinary IL-16 (u-IL-16) was higher in patients with active lupus nephritis and may be useful in differentiating patients with proliferative lupus nephritis from those with less severe LN subtypes and urinal SLE (11).

Serum uromodulin was lower in patients with renal activity and may be predictive of the risk of a renal flare (12). Similarly, beta 2-microglobulin correlated with BUN, serum creatinine and 24-h urinary protein.

Finally, galactin-3 binding protein was higher in proliferative and membranous SLE nephritis, but not in patients with mesangial form and correlated with activity in renal biopsies (13).

Chemokine ligand 21 (CCL21) and interferon gamma-induced protein 10 (IP10) correlated with lung involvement and had high sensitivity (83.7%) and specificity (94.1%) in detecting pulmonary disease (14).

In addition to their diagnostic and predictive value in detecting organ involvement and disease activity, some biomarkers may be used in monitoring response to therapy. In a *post-hoc* analysis, it was seen that low regulatory T cells and skin rash may indicate good response to low-dose IL-2 treatment (15).

Take home messages

- CCL21 and IP10 may detect pulmonary involvement with high sensitivity and specificity (14).
- IFN-I pathway activation is detectable in almost all newly diagnosed SLE patients and a negative test for SIGLEC1 could help to exclude SLE in suspected cases (8).
- IL-33 and soluble ST2 levels are increased in SLE, and soluble ST2 may represents a surrogate marker of disease activity and complications of nephritis (10).

Clinical aspects and outcomes

SLE can affect various organs and tissues, and the clinical manifestations of lupus can range from mild to severe and may vary greatly from individual to individual. In 2019, for the first time, fever was included among the items of the EULAR/ACR classification criteria for SLE, due to its higher prevalence in lupus compared to mimicking conditions. In this regard, a retrospective study investigated the possible association of fever with other clinical disease manifestations (16), and the authors identified a specific disease phenotype characterised by fever, haematological involvement, serositis and more severe organ damage. In addition, the work provided new insights into the role of genetic background in the pathogenesis of SLE-related fever since an association between fever and the rs13361189 of the immunity-related GTPase M (IRGM) gene, codifying for a key autophagy protein, was found.

Within the framework of rare manifestations, a recent paper drew attention to six rare clinical conditions of SLE focusing on their frequency and clinical aspects (17). In most of the cases, it was confirmed that the selected disease manifestations were uncommon in SLE, except for gastrointestinal manifestations that were more frequent than expected, with a prevalence ranging from 0.5% to 10.7%. The rarest pulmonary manifestations identified were interstitial lung disease, lupus pneumonia and shrinking lung syndrome, reported in 4%, 3% and 1.5% of patients. Myocarditis and pulmonary hypertension have also been rarely described in SLE patients with a variable prevalence ranging from 0.4–16% and 1–14%, respectively. Ocular manifestations in SLE included some rare manifestations and lupus retinopathy, described in 1.2–28.8% of the cases. Finally, aseptic meningitis and chorea were confirmed to be rare manifestations, described in less than 1% of cases.

Renal involvement is one of the most severe and potentially life-threatening manifestations of SLE, and in 2022 several papers focused on LN and its evolution over time, with a particular emphasis on the development of long-term damage. A single-centre study including 37 patients at their first episode of biopsy-proven class III, IV, and/or V LN, estimated glomerular filtration rate trajectories in LN over 5 years following renal biopsy; 11 patients (30%) accrued progressive renal damage despite standard-of-care therapy and the

achievement of complete proteinuric response at one year (defined as <0.5 g/24 hours) (18). Comorbidities, histopathologic features, and treatment strategies did not significantly differ between patients with progressive renal damage and those without. In another study on 71 patients with biopsy-proven LN (19), the course of proteinuria, serum level of C3 and C4 and anti-dsDNA antibodies titre were found to be significantly associated with renal relapse within 10 years of follow-up, and decreased renal function at onset and the first year after diagnosis was predictive of impaired renal function during follow-up. From a histopathological point of view, it is well known that historically the LN classification based on renal biopsy has been used to distinguish various patterns of renal involvement. Meaningful research in this field has found new phenotypic forms of LN, thus surpassing the traditional classes included in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system. A study assessed the histopathology data obtained from 314 renal biopsies from the Belimumab International Study in LN trial (20). Class III was characterised by segmental endocapillary hypercellularity, class IVG by global hypercellularity, wire loops, hyaline thrombi and double contours and class IVS cases displayed intermediate characteristics. By cluster analysis, two main groups were distinguished and labelled as membranoproliferative-like (global endocapillary hypercellularity, wire loops, double contours and hyaline thrombi) and vasculitis-like (segmental endocapillary hypercellularity, crescents and fibrinoid necrosis). Cluster analysis revealed a new segregation of LN lesions that are potentially eligible for targeted and diversified immunosuppressive therapy (20).

The histological predictors of long-term outcome of LN were analysed in 61 repeated kidney biopsies 49 months after the first biopsy (21). Presentation with nephritic syndrome and serum creatinine ≥1.6 mg/dL at first biopsy predicted an increase in the chronicity index instead of induction treatment with any immunosuppressive therapy and cyclophosphamide tended to protect from an increase in the chronicity index. At the second kidney biopsy two different models – the first including activity index >3 and chronicity index >4 and the second model including moderate/severe cellular/fibrocellular crescents and interstitial fibrosis – predicted estimated a decrease in the glomerular filtration rate at multivariate analysis.

In the context of the patient's perspective, a new model grouped patients into two categories based on their symptom experiences, the Type 1 and 2 SLE model (22). Type 1 SLE included signs and symptoms classically attributed to inflammation such as arthritis, rash, serositis, nephritis, central nervous system lupus and certain laboratory findings. Type 2 SLE included fatigue, widespread pain, mood disturbance, and cognitive dysfunction. The authors observed that Type 2 SLE symptoms occurred almost invariably during the course of the disease and could have two distinct patterns: intermittent and in synchrony with Type 1 inflammatory symptoms, or persistent Type 2 symptoms despite remission of Type 1 symptoms. A second study identified clusters of SLE patients by analysing data collected from 1.376 patients with SLE via a cross-sectional survey (23). Latent-class cluster analysis identified four different groups, *i.e.* very mild, mild, moderate, and severe, based on the burden of symptoms across organs or areas of the body. The very mild cluster was characterised by skin involvement and the mild cluster by joint and skin involvement. The moderate and severe clusters exhibited more complex manifestations, cardiovascular involvement was more common in the moderate cluster, while renal/mental factor involvement was higher in the severe cluster. Patient-reported impact including health status, fatigue, work productivity impairment, anxiety/depression, and emotional impact increased with increasing cluster severity. Interestingly, the proportion of physicians and patients satisfied with treatment decreased with increasing cluster severity which indicated the highest level of unmet need in the severe cluster of patients (23). In addition, a cross-sectional observational study (24) demonstrated that patients with active disease were significantly more anxious and depressed compared to patients in low disease activity (LDA) state or remission. Symptoms of anxiety and depression had a significant negative impact on quality of life and perception of disease activity, regardless of other factors. Lastly, a study carried out by Costenbader *et al*. (25) has further contributed to this understanding. The authors investigated the association of SLE flares with patient-reported outcomes (PROs) and healthcare resource utilisation using real-world data. The analysis showed a significant and consistent association of flaring with a range of PROs in SLE patients. Flaring was also associated with worse FACIT fatigue scores, health status, greater impairment of work productivity and ultimately with healthcare resources.

Take home messages

- Definitions of lupus nephritis treatment response based on proteinuria may fail to identify a proportion of patients who continue to accrue renal damage despite apparent response to standard-of-care therapy (18).
- The long-term outcome of lupus nephritis is variable and depends on several factors, including baseline serum creatinine and initial immunosuppressive therapy. The role of repeated kidney biopsy seems to provide useful information on the long-term prognosis of lupus nephritis (21).
- Careful evaluation of the characteristics of SLE, depicted by different models or clusters able to encompass clinical features and symptom burden in different organs, is essential to address the unmet needs of lupus patients (22, 23).

Comorbidities and organ damage

The complexity of SLE refers not only to the multi-organ involvement linked with the disease itself, but also to the multifaceted connections that disease activity could have with pre-existing or incident comorbidities.

Frailty is defined as a loss of physiologic reserve arising from the accumulation

of health deficits over-time. A recently developed SLE-specific frailty index (SLICC-FI) was externally validated in the Dalhousie Lupus Clinic Registry (26). The authors confirmed that patients with established SLE judged as frail at baseline had a significantly higher mortality risk during follow-up compared with those who were not frail. Similarly, SLICC-FI changes predicted changes in damage over time. The complexity of SLE is also revealed in polypharmacy assessment. Polypharmacy was investigated taking advantage from the Manitoba Drug Program Information Network in 206 patients from a tertiary care rheumatology clinic from Canada (27). Polypharmacy was common, since 72% of patients filled ≥5 medications, and 35% filled ≥10 medications, with higher percentages than those reported for equivalent age groups in the State under evaluation. Polypharmacy was associated with Charlson Comorbidity Index (CCI) score and GC use, and these studies suggest possible ways of homogenising reporting of comorbidities burden in SLE.

A large-scale retrospective study from China evaluated the overall cancer risk in patients with different autoimmune diseases. The standardised incidence ratio (SIR) for cancer development was lower for SLE (2.58) with respect to the other diseases, but SLE patients had significantly increased SIRs for developing haematologic malignancies and solid tumours of the urinary bladder (28). A huge population-based study using health-record databases on 19 autoimmune and 12 cardiovascular (CV) diseases in the UK stated that patients with autoimmune diseases have approximately a 1.4–3.6 times higher risk of developing incident CV diseases with respect to people without an autoimmune disorder; this order of magnitude resembles the risk caused by diabetes, indicating a pattern that affects autoimmune disorders as a group of diseases, rather than individually (29). Similarly, autoimmune patients share a significantly increased risk of hospital admissions for and mortality from CV causes. Focusing specifically on SLE, this disease had one of the highest overall CV risks among all the autoimmune diseases evaluated (HR 2.82). These risks were not completely explained by traditional CV risk factors. As stated by the recently released EULAR recommendations (30) for CV risk management in rheumatic and musculoskeletal diseases, CV risk assessment and management count as a priority in the evaluation of autoimmune syndromes. Moreover, given that hydroxychloroquine (HCQ) should be administered to all SLE patients unless contraindicated, a cross-sectional study from the Spanish Society of Rheumatology Lupus Register (RELESSER), with over 3,500 patients, confirmed the cardioprotective role of antimalarials (AM) with respect to the risk of chronic heart failure (31).

One of the most important concepts related to comorbidities in SLE refers to organ damage. The independent impact that specific definitions of remission or LDA could have on damage accrual has been explored in a large multinational disease inception cohort, the Systemic Lupus International Collaborating Clinics (SLICC) cohort (32). In this study, the authors analysed the outcomes related to 1,652 patients, applying the most stringent definition per visit. Each definition was associated with less damage accrual, even adjusting for confounders, suggesting that remission should be encouraged, but LDA could be good alternative target. Moreover, the time spent in remission or LDA state was associated with better outcomes. These data were confirmed in another study performed exploiting the Asia Pacifc Lupus Collaboration (APLC) cohort (33). Never attaining LDA, a time-adjusted mean SLEDAI-2K>4, or ever experiencing high disease activity status (SLEDAI-2K ≥10) were associated with damage accrual, as well as with increased mortality rates. The trajectories of damage items of the SDI in African American or White ethnicities in a large prospective SLE cohort (2,436 patients) were analysed by Kallas *et al*., who confirmed that African Americans accrued more damage and at a faster rate compared to White patients (34). For most organs, the difference persisted after adjustment for socioeconomic status.

Take home messages

- Comorbidities are key parts of the complexity of SLE disease, but heterogeneity in reporting still limits the full comparability across studies. The assessment of frailty could help to uniformly characterise the overall damage and mortality risks (26).
- Cardiovascular (CV) risk is increased in SLE patients with respect to general population, and CV risk assessment should be prioritised in the management of autoimmune diseases (29).
- Damage accrual could be prevented, or at least decelerated, by ensuring adequate disease control in SLE, and this could refer not only to remission achievement, but even to LDA maintenance status (32).

Treatment: new targets

New discoveries on the pathogenesis of SLE have enabled the development of potential new molecules and technologies studied both in animal models and through phase 1 trials.

In vitro and pre-clinical studies

An important role in autoantibody formation is played by the major histocompatibility complex (MHC) class II. Kawato *et al*. (35) studied the efficacy of ASP1617, a Cathepsin S (CatS) inhibitor molecule, on both human and murine B cells. This new drug reduced the expression of MHC II on the surface of both human and mouse B cells, and orally administered ASP1617 resulted in suppression of anti-dsDNA IgG antibodies, prevented progression of lupus-like glomerulonephritis and significantly reduced proteinuria levels, while mycophenolate moefetil (MMF) did not suppress anti-dsDNA IgG levels.

During the past year, several studies aimed to find new molecules capable of targeting LN. The effects of SB431542, a selective inhibitor of the TGFβ type I receptor were tested in mouse models (36), and an improvement in proteinuria, renal function, and histological findings was recorded. In addition, downregulation of genes involved in B-cell activation, proliferation, differentiation and receptor signalling processes was observed as well as a reduction in

serum levels of IgG anti-dsDNA antibodies and in splenic or renal levels of CD20.

In another interesting study, the effect of HSPB5, small heat shock protein (HSP) involved in reducing inflammation and tissue damage, was described (37). The study was conducted in a mouse model, and HSPB5 resulted to increase splenic levels of T and Bregs and to reduce inflammation and renal damage, with comparable effect and in some cases superior to those of methylprednisolone.

Targeting miR-21 may be a potential therapeutic strategy for patients with SLE, since promising results of antagomir-21, an inhibitor of miR-21, were recently described. This drug significantly reduced expansion of follicular helper T cells that support B cell development, germinal centre formation and antibody production with improving in skin lesions and nephritis in MRL/lpr mice (38).

Phase 1 trials

Two sequential, randomised, phase 1 studies (39) verified the safety and tolerability of NKTR-358, a polyethylene glycol-interleukin-2 conjugate composition that aims to induce regulatory T cells (Tregs). NKTR-358 was found to be well tolerated and achieved the goal of markedly increasing the number of CD25 Tregs without altering other T cells.

Among the various new possible therapies studied for the treatment of SLE, the possible use of mesenchymal stromal/stem cells (MSCs) has aroused a great deal of interest. In a recent study (40) adult patients with biopsy-confirmed LN who were refractory to standard treatment were treated with administration of adipose-derived alloMSCs (AD-MSCs). No major adverse events (AEs) were observed, and a significant reduction in urinary protein levels in the first month post-intervention was found, although the levels remained below baseline until the third month. A similar trend was also found in SLEDAI, with a reduction until the 6th month post-therapy and an increasing at 12th month, indicating that multiple administrations over time may be needed to maintain adequate remission over time.

The possibility of using drugs already licensed for other diseases for their possible beneficial properties in SLE has been the subject of several studies. Among them, the possible use of dapagliflozin, an SGLT2 inhibitor, was studied in a single-arm open-label phase I/II trial (41) that showed an acceptable safety profile in SLE patients, but no effects in terms of reduction of disease activity or proteinuria in cases of LN patients.

Take home messages

- ASP1617, a Cathepsin S inhibitor molecule, has shown encouraging results as a potential new therapeutic agent for SLE (35).
- Promising results for lupus nephritis treatment are coming from the development of new molecules such as SB431542 (36) or HSPB5 (37).

Treatment: clinical trials and drug discovery

Development of safe and effective treatments for patients with SLE still represents a challenge. High placebo responses have been observed in studies, and safety concerns still emerge in the management of SLE patients, since many of them have unacceptable toxicity from current treatment options (42). In the last year, important evidence emerged on the long-term safety profile of drugs already used in the management of SLE patients.

Particularly, the integration of data from several randomised controlled trials (RCTs) has allowed to further explore the safety of belimumab.

Wallace *et al*. performed a pooled *post-hoc* analysis of 52-week safety data from one phase 2 and five phase 3 belimumab trials in adult patients with SLE (43), including 4170 patients.

The overall incidence of AEs was similar in the placebo and belimumab groups, except for a slightly higher proportion of post-infusion/injection systemic reactions in the belimumab group (10.2% *vs*. 8.1%). A similar proportion of patients experienced AEs and serious adverse events (SAEs) considered related to the study drug. This large integrated analysis makes belimumab one of the most highly studied drugs for safety in the treatment of SLE. Moreover, supporting the good benefit/risk profile of belimumab, no new safety signals were identified in the open-label extension of BLISS-LN Study in patients with LN (44).

Interestingly, van Vollenhoven *et al*. (45) have reported the final efficacy and safety results through 2 years from the open-label extension of a phase 2 study evaluating ustekinumab in SLE. Clinically meaningful improvements in global and organ-specific SLE activity measures were observed. Through week 120, 86% of all patients treated with ustekinumab had at least one AE, most frequently infections; 17 patients treated with ustekinumab had a SAE. No deaths, malignancies, opportunistic infections, or tuberculosis cases occurred.

Undoubtedly, this last year has been characterised by growing evidence on the role of anifrolumab in the treatment of active SLE.

The *post-hoc* analysis of pooled data from the two Phase 3 RCTs (TULIP-1/2) of intravenous anifrolumab supported the consistent efficacy of anifrolumab across different subgroups of patients with SLE. In particular, subgroups with larger treatment differences included: IFNGS-high patients (18.2%), patients with abnormal baseline serological markers (23.1%) and Asian patients (29.2%) (46).

Moreover, data from the extension study in patients with SLE who completed the TULIP trial confirmed the safety profile of anifrolumab (47), and the incidence rates of AEs and SAEs were all comparable between the anifrolumab and placebo groups.

Data on efficacy of anifrolumab in LN appear to be less encouraging. In the Phase 2 TULIP-LN trial, patients were randomised to receive monthly intravenous anifrolumab basic regimen (300 mg), intensified regimen (900 mg×3, 300 mg thereafter) or placebo, alongside standard therapy. The primary endpoint was not met however, numerically more patients treated with anifrolumab intensified regimen *versus* placebo attained complete renal

response (CRR) and sustained glucocorticoid reductions (48).

These recent data underline that the treatment of LN remains challenging.

Furie *et al*. published the results of the RCT on the use of obinutuzumab (NOBILITY) (49), a humanised type II anti-CD20 antibody, *versus* placebo for the treatment of proliferative LN in combination with standard therapies. Achievement of CRR was greater with obinutuzumab at week 52 (35% *vs*. 23%) and at week 104 (41% *vs*. 23%). The treatment effect of obinutuzumab appeared to be greatest among patients with high levels of proteinuria at baseline and those with class IV LN.

obinutuzumab resulted in rapid and potent depletion of peripheral CD19+ B cells without an increase in the incidence of SAEs, infections or death compared with placebo.

Cutaneous lupus (CLE) represents a very impactful disease manifestation from the patient's perspective and successful treatments for cutaneous lesions are still lacking.

Activation of the IFN pathway seems to be a key driver of cutaneous lupus disease activity. Therefore, apart from the growing evidence on the efficacy of anifrolumab on skin manifestations, new molecules targeting the IFN pathways have been studied.

Treatment with litifilimab, a monoclonal antibody targeting blood dendritic cell antigen 2 (BDCA2) on plasmacytoid dendritic cells, has been studied for cutaneous and systemic lupus, showing to reduce the expression of IFN-I response biomarkers in blood and skin. In a Phase 2 trial treatment with litifilimab resulted superior with respect to the measurement of cutaneous activity (CLASI-A) (50).

Subsequently, litifilimab was also studied in patients with SLE with negative results in terms of efficacy and safety (51).

Werth *et al*. (42) have recently published the results of a phase 2, proof-of-concept RCT on the use of lanraplenib, a spleen tyrosine kinase (SYK) inhibitor, and filgotinib, a preferential JAK1 inhibitor, in patients with active cutaneous lupus. The primary endpoint was not met. However, filgotinib treatment resulted in a trend suggesting improvement in skin manifestations of CLE compared to placebo in subgroups of patients with more severe manifestations. Therefore, these results collectively suggest that JAK1 inhibition in CLE warrants further investigation while SYK inhibition does not.

Encouraging results appear to come from the study of deucravacitinib, a tyrosine kinase 2 inhibitor, in a phase 2 RCT of patients with active SLE. Deucravacitinib treatment elicited higher response rates for SRI-4 at W32 and the safety profile was acceptable (52).

Another new molecule that is being evaluated for the treatment of SLE is iberdomide, a cereblon modulator promoting degradation of the transcription factors Ikaros and Aiolos, which affect leukocyte development and autoimmunity. In a phase 2 trial (53) iberdomide at a dose of 0.45 mg yielded a higher percentage of patients with an SRI-4 response than did placebo. Iberdomide-associated AEs included urinary tract and upper respiratory tract infections and neutropenia.

Finally, in the LUPIL-2, a multicentre RCT phase 2 trial, the potential benefit of low-dose interleukin-2 (IL-2) therapy in active SLE has been evaluated (54), however, the primary end point was not met.

Take home messages

- In the last year, pooled *post-hoc* analysis and long-term data from randomised control trials have confirmed the benefit/risk profile of belimumab (43, 44) and the growing role of anifrolumab (46-48) in the treatment of moderate-to-severe SLE.
- Cutaneous manifestations emerge as an important unmet need in the management of the disease and data from phase 2 trials particularly targeting the IFN and JAK pathways in patients with cutaneous and systemic lupus have been published with conflicting results (42, 50, 51).

Treatment: real world evidence

In a recent paper (55), the use of medications and the treatment persistence were described showing that triple therapy with AM, GCs e IS was the most frequent pattern in a large cohort. Analysis of time-to-discontinuation revealed a very large variability and patients with active disease had lower discontinuation of GC, higher discontinuation of IS and were more likely to receive more medications. Overall, these data underlined that SLE management is still complex and variable.

Drug discontinuation

The question regarding the effects of therapy withdrawal in SLE patients who achieved prolonged disease quiescence is becoming increasingly important, since more patients are achieving prolonged clinical remission and several papers have focused on this topic

The Glucocorticoids Use in newly diagnosed SLE Patients (GULP) study provided evidence on 127 SLE patients who started prednisone (PDN) ≥5 mg/day and concomitant AM or IS within 12 months of SLE classification (56). The probability of tapering PDN doses <5 mg/day was lower in patients with renal involvement and low C3 serum levels, while high European Consensus Lupus Activity Measurement (ECLAM) scores were associated with a greater probability of increasing GC dose, independently of daily intake.

The impact of GC discontinuation in SLE patients with prior severe organ was explored by Nakai *et al*. (57) in a retrospective analysis of 73 patients who underwent GC tapering; no significant differences were noted in flare rate at 52 weeks after GC discontinuation with respect to those without prior severe organ involvement. Hypocomplementaemia, elevated anti-dsDNA antibody titres, positive anti-Smith/anti-ribonucleoprotein antibody, and use of any IS at GC discontinuation resulted negatively associated with flare-free remission.

Papachristos *et al*. (58) analysed the flares rate in patients who withdrew AM after at least 1 year of remission in comparison with a control group of patients who continued AM therapy and achieved clinical remission for at least 1 year. This study showed that disease flares occurred in a significant higher percentage of the AM withdrawal group. Interestingly, in the AM

withdrawal group, patients who tapered therapy had significantly fewer flares with respect to those who ceased it abruptly. These data suggest that AM have a role in preventing disease flares even in patients who have achieved prolonged disease quiescence, and in cases of cessation a slow taper is warranted.

It is still unclear if and when to discontinue IS therapy in patients with LN in remission; rate and predictive factors for flare after IS withdrawal in a cohort of LN patients treated with IS have recently been described (59). 22.8% of flares was recorded in patients who discontinued IS.

HCQ maintenance therapy, age at IS discontinuation and remission lasting more than 3 years before IS discontinuation resulted protective against disease flares.

Belimumab

During the last year, several real-life evidence regarding the GC-sparing effect of belimumab has been also described.

In a retrospective study (60) the mean daily oral GC dose over the 3–6 months prior *versus* 6 months post first belimumab prescription was compared in 204 patients from the Rheumatology Informatics System for Effectiveness (RISE) Registry. In patients with extended follow-up, GC doses were also assessed 12 and 24 months after belimumab initiation. Only a modest change in mean daily GC dose after belimumab initiation was observed; however, some data such as disease severity were not taken into account, thus limiting the strength of the results.

Another retrospective observational study investigated the efficacy of belimumab as maintenance therapy in SLE patients with SLEDAI<10; 103 SLE patients on HCQ and/or MMF alone were compared with 100 SLE patients on HCQ and/or MMF plus belimumab. At 52 weeks of follow-up, daily GC dose and relapse rate were significantly lower in the belimumab group and lower GC doses at baseline were associated with GC dose-tapering and discontinuation (61).

Others

In relapsing or refractory SLE patients who had received at least one course of rituximab (RTX) induction, a multicentre prospective cohort study was conducted to compare the efficacy and safety of RTX *vs*. traditional IS as maintenance therapy (62). Of 67 patients who had a clinical response at 6 months, 50.7% received RTX maintenance therapy, while the other 49.3% IS maintenance therapy. After a median follow-up of 24 months, 3 patients in the RTX group and 10 in the IS group developed a flare; patients in the RTX group also had a higher relapse-free survival rate. HCQ use, RTX maintenance therapy, and haematological system involvement were independent predictors for sustained remission. Therefore, long-term RTX maintenance therapy seems to have high efficacy and acceptable safety in these groups of patients.

Another real-world cohort study was conducted to compare the effectiveness and safety of sirolimus (an inhibitor of the mechanistic target of rapamycin) with respect to tacrolimus in clinically active SLE (63). Data on 104 patients (52 in sirolimus group and 52 in tacrolimus group) were collected, and a comparison between the two group was performed every 3 months until the year-1 follow-up. The results indicated that sirolimus had similar effectiveness with respect to tacrolimus but had better effects on serological improvement and GC tapering. Although more AEs were observed in the sirolimus group (17 *vs*. 3), none was severe or led to discontinuation of sirolimus.

Take home messages

- Most SLE patients receive a combination treatment, and the association of antimalarials (AM), glucocorticoids (GC) and immunosuppressants (IS) appears to be the most frequent pattern (55).
- GC discontinuation seems to be possible with today's drugs (56, 57).
- AM therapy prevents disease flare even in patients who have achieved prolonged disease remission (58).

Precision medicine

Precision medicine consists of a tailored approach to each patient based on genetic and epigenetic profiles, and the topic has aroused great interest also in SLE. Several studies aimed at identifying markers able to predict response to specific drug were recently published.

Beltrán-Ramírez *et al*. analysed macrophage migration inhibition factor (MIF) and P-glycoprotein (P-gp) serum levels in SLE and healthy controls (64) showing that MIF and P-gp could be related to steroid resistance in SLE patients. Another study (65) identified single nucleotide polymorphism and copy number variation for genes encoding five Fc gamma receptor (FcγRs) to evaluate RTX response in SLE and rheumatoid arthritis. The results showed that FcγRIIIa was the major low affinity FcγR associated with RTX response.

To identify baseline immunophenotypes that may predict the response to AM therapy, Patel *et al*. (66) performed mass cytometry imaging of immune cell types and inflammation markers in treatment-naive skin biopsy samples from 48 patients with CLE (CLE). HCQ responders had increased $CD4^+$ T cells respect to the quinacrine (QC) responder group, while non-responder group had lower Treg cells compared to QC responders and increased central memory T cells compared to HCQ responders.

Garantziotis *et al*. (67) used a RNA-sequencing dataset to stratify lupus patients according to underlying molecular aberrancies and predict personalised therapeutic strategies. They identified 5 lupus endotypes corresponding to different clinical phenotypes: G1 "Haemostasis" group, G2 "Autophagy" group, G3 "Metabolism" group, G4 "Neutrophil" group, and G5 "B cell" group.

An interesting study presented Epione application (68), a web-toolkit which makes it possible to identify the most reliable gene variants and single nucleotide polymorphisms (SNPs) associated with SLE susceptibility, using patients' genomic data. The Epione database may help physicians in early-stage diagnosis of SLE.

Lastly, Toro-Domínguez *et al*. (69) developed a scoring system able to evaluate the personalised Molecular dysregulated PROfiles of SLE patients (MyPROSLE) which enables the identification of the molecular fingerprints

involved in SLE activity in individual patients. Almost 6100 lupus and 750 healthy samples were analysed to assess the association between dysregulation scores, clinical manifestations, outcome, flare and remission events; the study found that dysregulation of some gene-modules was significantly associated with specific clinical manifestations, the occurrence of relapses or long-term remission and drug response.

Take home messages

- In a precision medicine perspective, SLE treatment would be based on the genetic profiles of individual patients related to pathogenesis and response therapy (64-66).
- Fingerprints are important tools that allow stratifying patients into groups with similar biological disease profiles (69).
- Computer programmes could be useful in supporting clinicians to stratify patients with similar genetic characteristics and similar pathogenetic pathways (68).

COVID-19 and other infections

Infections are still a major cause of morbidity and mortality in SLE, especially in the early stages of the disease. Wang *et al*. found major infections in 14% of the Chinese inception cohort of 494 newly diagnosed hospitalised SLE patients, with most events occurring in the first 4 months of the disease (70). They then developed a prediction model to identify patients with newly diagnosed SLE at risk of major infections. Interestingly, this model maintained its validity after adjustment for GC exposure and IS therapy, suggesting that disease activity outweighs the impact of treatment on early infection risk.

According to data from the Spanish national registry, infections were the cause of death in 25% of hospitalised SLE patients, a significantly higher rate than what was observed in the general Spanish population (8%), especially at a younger age (71). The greatest differences were found in relation to respiratory tract infections, sepsis and viral infections, emphasising the need for measures to mitigate the impact of infections in these patients.

In a cohort of SLE patients prospectively followed in an Australian tertiary centre, Ko *et al*. identified higher SDI scores, higher disease activity and the use of cyclophosphamide as predictors of a first severe infection (defined as requiring hospitalisation), with a history of previous serious infection conferring the highest risk for repeated episodes (72). Conversely, being in LDA and length of time in LDA were associated with lower risk of severe infection.

The pathways involved in the host immune response against infections may be dysregulated in autoimmune diseases. From a genetic point of view, while some alleles at risk for SLE were also found to be at risk for severe forms of COVID-19, the Janus-kinase locus TYK2 showed opposite effects in the two conditions (73). At this level, SLE risk alleles mitigate the outcome following SARS-CoV-2 infection.

In addition to demographic factors and comorbidities already reported in the general population, the use of GCs, as well as untreated or active SLE and therapy with RTX, MMF and cyclophosphamide, have been associated with more severe COVID-19 outcomes according to data on over 1600 cases in SLE patients from the COVID-19 Global Rheumatology Alliance registry (74). Moreover, in the United States, Black and Hispanic people with SLE experienced poorer COVID-19 outcomes with respect to White individuals (75).

Kwan *et al*. reported a prevalence of Herpes Zoster (HZ) infection of 30.5% in a Canadian cohort of 422 patients with SLE, based on a patient-reported questionnaire constructed to capture HZ features (76): a significant association between HZ events and lymphopenia, as well as with GC dosing was found. Furthermore, this study confirmed HZ infection as a late complication in the course of SLE, with a mean disease duration at the time of the first HZ infection of 12.5years.

The IFN pathway plays a key role in both SLE and viral infections. Recently, consistent with previous studies, Mathian *et al*. found a prevalence of 11.7% of neutralising and non-neutralising anti-IFNα autoantibodies in a monocentric French cohort of 609 SLE patients (77): if on the one hand the presence of neutralising autoantibodies seemed to be associated with reduced SLE disease activity, on the other hand it seemed to increase the viral infection risk in these patients. Indeed, SLE patients with neutralising anti-IFNα autoantibodies more often had a history of severe or critical COVID-19 pneumonia, cutaneous HZ and serious viral infections. Thus, monitoring anti-IFNα antibodies could help identify SLE patients at major risk of developing severe viral infections. In another paper (78), high titre of anti-IFNα was found to be protective against disease flare but seems to predispose to COVID-19, and IFNα production induced by SARS-Cov-2 may contribute to lupus flare bypassing the protective role of anti-IFNα.

With regards to AM therapy, an association between HCQ and QT prolongation in COVID-19 patients has been reported. Unlike COVID-19 patients, SLE patients under HCQ treatment do not seem to be susceptible to HCQ-induced long QT syndrome, suggesting that this difference could be due to the combined effect of arrhythmogenic effect of SARS-CoV-2 infection and HCQ in COVID-19 patients (79).

In another work Chen *et al*. demonstrated that the ectoenzyme CD38 regulates mitochondrial fitness in SLE $CD8^+$ T cells through the inhibition of mitophagy and reduces their function and response to viral infection, suggesting CD38 inhibition as an option to improve infection rates and outcome in SLE (80). In fact, they showed that administration of the CD38 inhibitor MK-0159 reverses mitochondrial defects and restores $CD8^+$ T cells function against infections in mice.

While data from the literature are sometimes conflicting on the actual impact of certain immunosuppressive drugs on infectious risk, there is consensus on the role of steroid therapy. While it is well known that daily doses of prednisolone ≥7.5 mg are a risk factor for infection, according to a prospective cohort study on 509 patients from the Japanese SLE registry, even lower doses of prednisolone would increase the infectious risk (81). In particular, the incidence of infection was significantly higher in the

group taking 5–7.5 mg of prednisolone with respect to the 0–2.5 mg group, underlining the need to reduce the use of systemic steroids in these patients as much as possible.

Identification of infections, particularly in the early stages, often remains challenging for physicians as they can mimic disease manifestations. Significantly higher values of serum C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were observed in infected SLE patients compared to the mixed group (both infection and disease activity) and to the group with isolated disease activity (82). Using these three parameters, the authors developed a clinical algorithm that showed good sensitivity and specificity for the diagnosis of infection.

Take home messages

- Infections in SLE and are linked not only to immunosuppressive therapy but also to disease activity, especially early in the course of the disease (70, 71).
- Early identification and treatment of infections, as well as the identification of individuals at higher risk, are essential, also in light of the new therapeutic strategies emerging in interferon-driven diseases such as SLE (77).
- To minimise the infectious risk, it is particularly important to obtain good control over disease activity, reducing the daily dosage of GCs as much as possible (81).

Reproductive health

SLE usually occurs in women of childbearing age, affecting fertility, family planning, and pregnancy course.

Ovarian reserve is an important biomarker of reproductive potential, and anti-Müllerian hormone (AMH), ovarian volume, and total antral follicle count were found to be lower in SLE patients compared with healthy controls (83). Moreover, these alterations were correlated with age, disease activity and damage accrual, confirming the negative impact of the disease on ovarian reserve.

Ghrelin was also described as a potential biomarker for ovarian reserve in SLE, and levels of this hormone were significantly lower in obese SLE patients than non-obese SLE patients and obese controls (84). In addition, ghrelin levels positively correlated with AMH, suggesting that it may play a part in energy homeostasis and ovarian damage in SLE patients.

Data on microchimerism in SLE patients and its relationship with pregnancy were recently published (85). Microchimerism was detected more often in non-pregnant SLE patients than control subjects, and pregnant patients were found to have a significantly higher median number of foetal chimeric cells in the granulocyte fraction just after delivery. Another interesting finding was that microchimerism reappeared years after the last pregnancy, more often and at higher levels in SLE-patients, suggesting that these chimeric cells may originate from non-circulating foetal chimeric stem cells.

Pregnancy outcome and treatment

In a Greek cohort of 82 pregnancies in SLE patients (86), 53.7% were complicated with at least one adverse pregnancy outcome (APO), and antiphospholipid antibody (aPL) positivity, persistent disease activity and GC intake during pregnancy were risk factors for APO. On the other hand, LDA at pregnancy onset was found to be protective against foetal complications.

Pathogenic changes in the placenta during pregnancy can play a role in maternal and foetal morbidity, and different expression of genes involved in the regulation of angiogenesis, cellular response to growth factor stimulus, heparin-binding, HIF-1, and IL-17 signalling pathway in SLE patients *versus* healthy controls were described (87).

Maternal GC exposure increases the risk of preterm delivery, but the association between GCs and preterm premature rupture of membranes (pPROM), a direct cause of preterm delivery, has rarely been investigated. In a recent study (88), it was found that the average GC dose in cases of pPROM in SLE patients was significantly higher than in those without pPROM. In addition, GC-treated amnion mesenchymal cells showed increased permeability and overexpression of ITGA8, a primary molecule that triggers pPROM through fibrotic remodelling and prevents resealing of the rupture site in foetal amnion.

Congenital heart block (CHB) is a rare autoimmune-mediated disease due to the transplacental passage of maternal autoantibodies anti-Ro/SSA and anti-La/SS-B, which injure the previously normal foetal heart. A recent study from the French Neonatal Lupus Syndrome registry (89) investigated short- and long-term outcomes of 215 mothers of offspring with CHB. One-quarter of the patients had an autoimmune disease diagnosis at the time of the foetal CHB diagnosis, mainly SLE and Sjögren syndrome, while about half of those without an initial diagnosis developed an autoimmune disease during follow-up, mostly without severe manifestations.

With regards to treatment during pregnancy, it is still a matter of debate whether low-dose acetylsalicylic acid (LDASA) should be prescribed to all patients with SLE during pregnancy. A multicentre study (90) has investigated the impact of LDASA on pregnancy outcomes in patients with SLE with no history of renal involvement and or aPL. The incidence of APO was similar in pregnancy exposed and not exposed to LDASA. Notably, pre-eclampsia was more infrequent in patients taking LDASA (2.4% *vs*. 8.3%) but the difference did not reach statistical significance.

Another study (91) explored the effects of HCQ alone and in combination with LDASA (HCQASP) in pregnant women with SLE. The HCQASP group had a significantly higher proportion of full-term pregnancies, higher birth weight and Apgar scores, and a significantly lower proportion of hypertension, prematurity, and pregnancy loss than the HCQ group.

Patients' point of view

Reproductive concerns are common in women of childbearing age with systemic autoimmune diseases, and several studies have recently dealt with these concerns and the patients' point of view. In a Chinese monocentric cross-sectional study (92), validated questionnaires were used to investigate reproductive concerns in SLE patients. The results

of "Reproductive Concerns After Cancer" questionnaire, which assess 6 areas of concern, indicated that women with SLE were more concerned about child's health and personal health than about becoming pregnant, fertility potential, partner disclose and acceptance. In addition, living in a rural context, having no experience of pregnancy, fearing unexpected pregnancy, having sexual distress and depression were associated with more serious fertility concerns.

In a recent European work (93), patients' unmet needs regarding pregnancy and family planning were analysed using the narrative-based medicine approach. The replies were collected from patients with rare and complex connective tissue diseases (CTDs), including 44 SLE patients. Fragmentation of care among different centres, lack of education and awareness of CTDs among non-expert healthcare professionals and lack of appropriate information and psychological support were found to be the unmet needs.

Take home messages

- Anti-Müllerian hormone (83) and ghrelin (84) seem to predict reproductive potential in SLE.
- Pathogenic changes in the placentas are described in SLE patients (87), and GCs appear to induce the expression of ITGA8 on amnion mesenchymal cells, triggering pre-term premature rupture of membranes (88).
- Low-dose acetylsalicylic acid treatment during pregnancy was not found to be protective against obstetric complications in SLE patients without aPL or history of renal involvement (90).

Conclusion

Over the past year, new and interesting papers on SLE have been published and the most relevant data on pathogenesis, clinical and laboratory aspects, comorbidities, infections, precision medicine and treatment novelties have been summarised in this review. All these data have improved the understanding of SLE, although further studies and research are needed to improve the knowledge we have on this complex disease.

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