Review

One year in review 2020: systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a relapsing-remitting course that can affect various organs or systems, leading to a broad spectrum of clinical manifestations.

In the past year, many studies have been published on SLE, providing a significant advancement in disease knowledge and patient management. The aim of this review is to summarise the most relevant scientific contributions on SLE pathogenesis, clinical manifestations and comorbidities, biomarkers and treatment strategies published in 2019.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a highly variable course and prognosis. Following the previous *One Year in Review* of this series (1-3), we hereby updated the overview of the new insights in the pathogenesis, clinical and laboratory finding as well as treatment and comorbidities. We performed a Medline search for English language articles published from 1st January to 31st December 2019 using MESH terms and free text words for the following search keys: systemic lupus erythematosus AND pathogenesis, biomarkers, clinical manifestations, comorbidities, therapy. We reviewed all the articles, selecting the most relevant papers on adult SLE and excluding review papers.

Pathogenesis and new therapeutic targets

Innate and adaptive immunity: role of interferon and neutrophils

In the last 12 months, key findings in the pathogenesis of systemic lupus erythematosus (SLE) reinforced the role of interferon (IFN) and of activated neutrophils in the disease-driving mechanisms. In lupus blood and tissues, there is an intense expression of IFN-I-induced gene transcripts; this genomic signature seems to be responsible for many of the immunologic and pathologic features of the persistent self-directed immune reaction. Among possible cellular pathways that could induce type I IFN response in SLE, we find the endosomal Toll-like receptors (TLRs), particularly TLR7, and the cytosolic sensors of DNA or RNA that engage the adapter STING (stimulator of interferon genes) (4). Kim *et al*. used a mouse model of SLE to investigate the role of mitochondrial stress in triggering the IFN-I production. They focused their study on the voltage-dependent anion channel (VDAC), the most abundant protein in the mitochondrial outer membrane. VDAC regulates Ca2+ influx, metabolite entry and exit and, ultimately, cell death. They found that conditions of mild stress, induced by host or environmental factors (including microbial infections), promoted mitochondrial DNA damage and fragmentation. The interaction of these fragments with VDAC induced its oligomerisation and pore formation; therefore, mitochondrial DNA fragments were able to enter the cytosol and activate the sensor cGAMP synthase, inducing a STING-mediated type I IFN inflammation (5). Furthermore, VDAC oligomerisation increased mitochondrial reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) release, two proposed important triggers for autoimmunity, in both humans and mice.

In this respect, growing evidence suggests that neutrophil dysregulation is implicated in the pathogenesis of SLE. A proinflammatory neutrophil subset identified in SLE and known as low-density granulocytes (LDGs) can synthesise and extrude NETs, chromatin fibres decorated with nuclear and granule proteins and oxidised nucleic acids inducing endothelial damage and vascular dysfunction. In SLE, NETs

stimulate the production of proinflammatory cytokines and type I IFN, promote immune cell maturation, and contribute to tissue damage and vascular dysfunction. Mistry *et al*. examined in detail the transcriptional, epigenetic, and functional profiles of lupus LDGs identifying 2 subpopulations: intermediate-mature and immature neutrophils. The maturation status of lupus neutrophil subsets affected their ability to perform critical functions including NET formation, chemotaxis, and phagocytosis; it was also associated with vascular damage and coronary plaque formation (6). Moreover, SLE LDGs exhibited an activated immunophenotype (concomitant expression of lectin-like oxidised low-density lipoprotein receptor-1 and CD63, a granulocyte activation marker) and were able to induce the production of proinflammatory cytokines such as IFNγ in $CD4^+$ T cells (7). The proinflammatory role observed in LDGs confirmed their potential pathogenic role in SLE. Finally, Frangou et al. elucidated the molecular mechanism underlying NET release and NET mediated end-organ injury in SLE. In sera of patients with active SLE, the expression of neutrophil hypoxia-response and stress-response protein DDIT4/REDD1 was upregulated, resulting in autophagy induction and subsequent NET release. NETs from patients with active renal and cutaneous lupus were decorated with tissue factor (TF) and interleukin (IL)-17A and were bioactive, inducing thrombin generation and activation/differentiation of human skin fibroblast to collagen-producing myofibroblasts. TF-bearing and IL-17A-bearing NETs were abundant in discoid skin lesions and in the glomerular and tubulointerstitial renal specimens, suggesting a link between thrombo-inflammation and fibrosis in SLE (8).

Genetic factors

A novel genetic link between protein citrullination and NETs provided further support for this pathway in SLE. Genetic variations of A20 (a negative regulator of NF-κB) deubiquitinase (DUB) domain presented an upregulated expression of PADI4, an enzyme involved in protein citrullination and NET formation (9). A Swedish study characterised the effect of single nucleotide polymorphism in the NCF1 gene (neutrophil cytosolic factor 1, NCF1-339, rs201802880), encoding NADPH oxidase type II subunit NCF1/p47phox, a multicomponent enzyme that, when activated, produces superoxide anion; another observation was that neutrophils from patients with NCF1-339 genotype displayed decreased levels of extracellular and intracellular ROS, impaired NET formation, high serum type I IFN activity, antiphospholipid antibody (aPL) positivity and secondary antiphospholipid syndrome (10).

Finally, a study explored the role of rare and low-frequency variants in BLK, a gene encoding a nonreceptor tyrosine-kinase involved in B-cell receptor signalling and B-cell development, and BANK1, a gene encoding a B-cell-specific scaffold protein. Exome sequencing of SLE-risk genes, performed in a European ancestry sample of 69 SLE patients and 97 healthy controls, showed that rare BLK and BANK1 missense variants contributed to risk. Moreover, in patients with BLK variants, the kinase activity of BLK was impaired, enhancing IRF5-mediated INF-β expression and production in human B cells (11).

Emerging potential therapeutic targets

Pre-clinical studies

Signalling lymphocytic activation molecule family members 1 (SLAMF1) are type I transmembrane glycoprotein cell surface receptors expressed on T cells, B cells, and dendritic cells that promote immunoglobulin production and T cell-B cell crosstalk. For their important role in modulating T cell–B cell interaction and B cell activation, SLAMF1 monoclonal antibodies are under examination for SLE. Karampetsou *et al*. showed that in the context of an *in vitro* T cell–B cell coculture system, SLAMF1 ligation with a SLAMF1 monoclonal antibody limited the frequency of IL-21 and IL-17A–producing $CD4^+$ T cells in healthy controls and patients with SLE. The authors suggested that this occurred through inhibition of direct interaction between T cells and B cells, and through modulation of B cell activation and BCR signalling, affecting the production of IL-6 by B cells (12).

Concerning the mitochondrial dysfunction as possible player in the immune dysregulation and organ damage in SLE, a study explored the role of a synthetic quinone, Idebenone, an analogue compound of the potent antioxidant coenzyme Q10, in two murine models of lupus. Idebenone-treated mice showed a significant reduction in mortality incidence ($p<0.01$ *vs*. untreated mice), and attenuation of several lupus features, including glomerular inflammation and fibrosis. Idebenone inhibited NET formation and improved mitochondrial metabolism. These preliminary data seem to support the therapeutic role of agents that modulate mitochondrial biologic processes in human SLE (13).

Phase 1 and 2 studies

A 36-week phase IIb, randomised, double-blind, placebo-controlled, multicentre study, assessed efficacy and safety of interferon-α kinoid in patients with active disease despite standard of care. Interferon-α kinoid is an immunotherapeutic vaccine composed of inactivated recombinant human IFN-α2b coupled to a T-helper carrier protein; the aim of its use is to induce, by active immunisation, antibodies against IFN-α. In this study, 185 patients with moderate to severe lupus and positive IFN gene signature were randomised to receive interferon-α kinoid or placebo. The interferon-α kinoid induced neutralising anti-IFN-α serum antibodies in 91% of treated patients and significantly down-regulated the IFN gene signature, achieving the biological endpoint. The clinical endpoint, that was the BILAG-Based Composite Lupus Assessment (BICLA) modified by mandatory corticosteroid tapering at week 36, was not met. However, a statistically significant and clinically relevant corticosteroid-sparing effect was observed in the IFN-K-group from week 28 onwards. Related adverse events were more frequent with interferon-α kinoid (40.7%) than with placebo (24.7%), whilst serious adverse event leading to permanent study drug discontinuation were more frequent in the placebo group (14).

A phase 1 and 2a trial assessed the safety and tolerability of low-dose recombinant human IL-2 (aldesleukin) and its effects on regulatory T cells. Eleven (92%) of the 12 patients achieved the primary endpoint defined as at least a 100% increase in the proportion of regulatory T cells at day 62 (after four treatment cycles). In ten (83%) of 12 patients, SELENA-SLEDAI scores were lower at day 62 than at baseline, and no severe disease flares were observed during the treatment period. Furthermore, decreased disease activity correlated with the magnitude of increase in the proportion of activated regulatory T cells. In this study, the most common adverse event was injection-site reaction, observed in 20% of patients (15).

In conclusion, among possible mechanisms involved in SLE pathogenesis, the most relevant findings emerged from studies that confirmed the important role both IFN and neutrophils dysregulation. In this regard, the Interferon-α kinoid, an immunotherapeutic vaccine developed to induce antibodies production against IFN-α, showed the most promising results.

Take home messages

- In lupus blood and tissues there is an intense expression of IFN-I–induced gene transcripts that seems to be responsible for many of the immunologic and pathologic features of the disease (4, 5); IFN-α inhibition showed promising results in early-phase clinical studies (14)
- A growing evidence suggests that neutrophil dysregulation is implicated in the pathogenesis of SLE (6-10)
- Signalling lymphocytic activation molecule family members 1 (SLAMF1) have an important role in modulating T cell–B cell interaction and B cell activation and they are under examination as potential treatment target in SLE (12)
- The coenzyme Q10 analogue idebenone improved mitochondrial metabolism and reduced Inflammation in a murine model of lupus (13)

Biomarkers

In the last year, several studies have been published about new emerging biomarkers that could help us to recognise early disease and could be correlated with systemic disease activity, organ involvement and treatment response.

Two Chinese studies hypothesised the possible role of circular RNAs (circRNAs) as biomarkers for SLE diagnosis. The first (16) demonstrated that levels of hsa_circ_0044235 and hsa_circ_0068367 in peripheral blood mononuclear cells (PBMC) were significantly increased in new-onset SLE patients and in patients who had positivity for anti-double-stranded DNA and anti-ribosomal protein P antibodies; the second one (17) identified circPTPN22 as possible diagnostic marker of SLE.

Moreover, a third Chinese study found a panel of five long non-coding RNAs (lncRNAs) as potential marker for SLE; this panel had high diagnostic accuracy and might distinguish SLE from rheumatoid arthritis and primary Sjögren's syndrome (18).

Another recent study demonstrated the possible role of serum beta-2 microglobulin (β2-MG) levels as marker of active disease. In particular, it was observed that serum β2-MG levels were significantly higher in SLE patients with articular, muco-cutaneous, renal and cardiac manifestations; therefore in active SLE patients, serum β2-MG levels positively correlated with SLEDAI and laboratory parameters (19).

New data also emerged on serum and urinary IL-17A; their levels correlated with disease activity in SLE, although both were neither sensitive nor specific as biomarkers to predict active disease (20).

An interesting study investigated the role of DTX1 in human T cell function; the results showed that DTX1 expression in the PBMC was significantly lower in SLE patients compared to healthy controls; a low DTX1 level induced high IFN-γ production and was associated with severe disease activity, in particular with active lupus nephritis (LN), lung involvement or hypocomplementaemia (21).

For LN, Rashad *et al*. (22) evaluated serum levels of Transforming Growth Factor Beta -1 (TGFβ-1). This protein is a member of cytokines family which has an important role in the pathogenesis of autoimmune diseases, including SLE. The results of this study showed that LN patients had significant lower values of serum TGF-β1 compared with non-LN patients ($p<0.001$), especially in class V LN, that demonstrated the lowest TGFβ1 serum levels.

Another possible LN biomarker is immunoglobulin binding protein 1 (IGBP1), a phosphoprotein associated with the B cell receptor (BCR) complex. One study observed that urine IGBP1 levels were increased in LN patients, and were correlated with the clinical activity and histological activity index (23).

Another study measured serum and urine levels of osteopontin (OPN) in patients with active LN (n=14), LN in remission (n=20), SLE without renal involvement (n=22) and healthy controls (n=20). Serum OPN levels were significantly higher in LN patients, when compared with healthy controls and SLE patients without renal involvement ($p<0.0001$ and 0.0032, respectively), regardless the phase of renal activity. Conversely, SLE patients without renal involvement and healthy controls showed similar serum levels of OPN (24).

Also serum soluble tumour necrosis factor receptor 1 (sTNF-R1) and urine vascular endothelial growth factor (VEGF) could represent useful markers of active LN: indeed, the median levels of these cytokines were higher in active LN patients, compared with inactive LN and non-renal SLE groups (25).

Many other cytokines could be considered markers of active LN. Among these, IL-17 was related to active LN, while IL-23 was correlated with a better response to immunosuppressive treatment in patients with active LN (26); also IL-32γ was associated with the activity and development of LN in SLE patients (27).

Considering the involvement of innate immune system in SLE pathogenesis, an American study characterised the phenotype of NK cells by multi-color flow cytometry in SLE patients; there was a higher expression of Ki67 on natural killer (NK) cells, with a strong correlation with clinical severity and active nephritis (28).

As far as neuropsychiatric (NPSLE) involvement is concerned, Kitagori *et al*. (29) measured OPN concentration in the cerebrospinal fluid (CSF) of SLE patients, finding that OPN levels were significantly higher in NPSLE than in non-NPSLE, and decreased after treatment; therefore, OPN could be a novel diagnostic biomarker of NPSLE. Another study found a positive correlation between CSF anti-ubiquitin carboxyl hydrolase L1 (UCH-L1) and severity of NPSLE (30).

Table I summarises the most relevant biomarkers and their possible role.

Table I. New emerging biomarkers and their correlation with global disease activity or organ specific involvement.

	Biomarkers	Disease activity	Renal Involvement	Neuropsychiatric Involvement	Reference
Serum	↑ β-Microglobulin	x			19
	↑ IL- 17A	x	x		20, 26
	↑ IL- 23		x		26
	↓ DTX1	x			21
	↓ TGFβ 1		x		22
	↑ IGBP1		x		23
	↑ OPN		x		24
	↑ TNF R1		x		25
	↑ IL 32γ		x		27
Urine	↑ VEGF		x		25
Cerebrospinal fluid	↑ OPN			x	29
	↑ U ‘ CH-L1			x	30

Take home messages

- A panel of circular RNAs (circRNAs) and long non-coding (lncRNAs) as diagnostic markers for SLE have been postulated (16-18)
- Serum levels of beta-2 microglobulin and IL-17A and DTX1 expression in peripheral blood mononuclear cells have been associated with disease activity (19-21)
- Osteopntin deserves a special attention as biomarkers of severe disease as it has been correlated with renal involvement as well as active neuropsychiatric involvement (24, 29)

Clinical manifestations

It is well recognised that both American College of Rheumatology (ACR) 1997 criteria (31) and Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria (32) have a limited accuracy in classifying patients with SLE: the first ones are highly specific but less sensitive, while the second ones are more sensitive but less specific. In this regard, Mosca *et al*. (33) analysed data collected from 389 patients with early SLE and 227 patients with SLE-mimicking conditions (including infections, lymphoma, other defined connective tissue diseases, primary aPL syndrome, UCTD, early rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, interstitial lung disease and fibromyalgia). The authors demonstrated a low sensitivity of ACR and SLICC criteria (66.1% and 83.5% respectively) and an unsatisfactory specificity (91.6 and 82.4% respectively) for an early and differential diagnosis.

With these premises, the European League Against Rheumatism (EULAR) jointly with the ACR recently proposed the new classification criteria (34). Original concepts are ANA positivity as obligatory entry criterion, and the additive, weighted multicriteria system. These new criteria apparently overcome the lack of specificity of SLICC 2012 criteria (93 *vs*. 84% in the validation cohort), maintaining a good sensitivity (96 *vs*. 97%).

Since criteria performance may be influenced by ethnicity and sex, we will need further studies in specific ethnical/racial subgroups and in male patients to determine the accuracy among wider populations. The same applies to paediatric SLE and organ-dominant disease.

As far as clinical manifestations are concerned, interesting data emerged on neuropsychiatric involvement. In clinical practice, neuroimaging is highly sensitive in detecting organic changes but not always specific, especially in distinguishing aPL ischaemic changes from other causes of cerebral vasculopathy. Magro-Checa *et al*. (35) investigated whether serum autoantibodies and traditional risk factors for cardiovascular disease (CVD) were associated with specific brain-MRI abnormalities. The results of this study showed that the most frequent findings were white matter hyperintensities (WMHs) and lacunar infarcts (LI); there was no correlation between the total number or the individual SLE-related autoantibodies (which included anti-dsDNA, anti-SSA, anti-SSB, anti-RNP, and anti-Sm) and inflammatory-like lesions on the brain-MRI; the total number of aPL was associated with ischaemic brain changes, mainly with lacunar infarcts (LA positivity), gliosis (aCL IgG positivity) and cerebral atrophy. Cumulative SLE-damage and hypertension were significantly associated with LI and WMHs+LI respectively, suggesting the importance of accelerated atherosclerosis in this process.

Hanly *et al*. analysed the frequency and attribution of Lupus Psychosis (LP) in a multiethnic, prospective inception cohort that included 1826 patients with a recent (<15 months) diagnosis of SLE. During follow-up (mean duration ± SD= 7.4±4.5 years), 52.1% of patients developed at least one neuropsychiatric (NP) symptom; of the 1902 unique NP events, 91.6% involved the central nervous system and 8.4% involved the peripheral nervous system. There were 31 psychotic events in 28 patients. In the majority of cases, psychosis was attributed to SLE (52–90% of events depending on the stringency of the model for causal attribution). Eighty percent of patients had their first episode either in the year prior to or within 3 years following the diagnosis of SLE. Significative associations with lupus psychosis were previous SLE NP events (HR 3.59), male sex (HR 3.0), younger age at SLE diagnosis (HR 1.45) and African ancestry (HR 4.59). The risk of LP was not associated to geographical location. In the univariate analysis, anti-P

antibodies were significantly associated to psychosis, but, similarly to earlier reports on NPSLE, the association was not confirmed after adjustment for demographic variables (36).

In conclusion, SLE remains a complex autoimmune disease characterised by variable clinical features and multiple autoantibodies. This variable presentation makes SLE a difficult disease to be diagnosed and classified. In this regard, the EULAR/ACR new classification criteria represent the most relevant finding over the last year.

Take home messages

- New classification criteria have been released that overcome the lack of specificity of SLICC 2012 criteria maintaining a good sensitivity (34)
- New data emerged on neuropsychiatric involvement for diagnosis and attribution of MRI findings (35) as well as for rare manifestations such as psychosis (36).

Comorbidities and organ damage

In the past decades there was been a significant increase in survival rate in SLE patients; therefore, patients live longer with the disease and have an increased risk to develop damage accrual and comorbidity, due to persistent disease activity and medications. Frodlund *et al*. (37) evaluated the damage accrual in a cohort of 543 patients using the SLICC/ACR damage index (SDI). More than half of patients (59%) developed at least a damaged organ (SDI ≥1). In the multiple regression model, damage accrual was higher in patients with Antiphospholipid Syndrome (APS), pericarditis, haemolytic anaemia, lymphopenia, myositis, chronic corticosteroids intake and antihypertensives drugs.

Osteoporosis (OP) and fractures are frequent complications in SLE patients and several causes can be recognised: among the others, chronic corticosteroid intake, systemic inflammation and reduced sun exposure can have a central role. Thus, in SLE patients fracture risk assessment is pivotal in order to set up appropriate preventive strategies. To assess the feasibility of Fracture Risk Assessment Tool (FRAX) in autoimmune diseases, Lai *et al*. (38) recruited 451 patients with rheumatoid arthritis (RA), 233 with SLE and 118 with primary Sjögren Syndrome (pSS). RA patients had the highest rate of bone fractures (43.0% of participants), followed by pSS patients (33.1%, 25% of which suffered from tubular acidosis) and finally SLE patients (29.2%). SLE patients experienced osteoporotic fracture at a younger age compared with the other two subgroups. FRAX score, with or without BMD, was accurate in predicting fracture risk probability in RA, but was inaccurate for pSS and SLE patients, even after adjustment by age and corticosteroid use.

In a recent meta-analysis on prevalence and risk factors of secondary OP, Gu *et al*. (39) selected 31 articles (cross-sectional or case-control studies), with a total sample of 3089 patients with SLE. Exclusion criteria for the meta-analysis included severe liver and kidney dysfunction, Cushing syndrome, history of thyroid and parathyroid diseases, ovariectomy and the use of drugs that affect bone metabolism. Compared to controls, SLE patients had a significantly higher risk of developing OP (OR= 2.03, 95% CI 1.33–3.10). Bone loss was reported in 16% of patients and was related to age, disease duration, cumulative glucocorticoid intake, duration of corticosteroid therapy, damage accrual, and menopause. Conversely, daily glucocorticoid dose, SLEDAI, and BMI were not significantly different in OP and non-OP subgroups.

Infections are another cause of hospital admissions and death in SLE patients. Torres-Ruiz *et al*.'s prospective study (40) evaluated baseline clinical and immunological features in a cohort of 55 SLE patients with less than 5 years of disease and then monitored the rate and type of infections that occurred during a 1-year follow-up. Infections occurred in 32.7% of patients. Major risk factors were immunosuppressant therapy, especially cyclophosphamide, but also immunological abnormalities such as B cell depletion, increased peripheral Th17 cells and lower TLR2 expression in monocytes. Using these data, the group created and validated a compound clinical-immunological index to predict the occurrence of infections in the short term. Specifically, a score >1.5 points was able to predict infection in the following year of observation (AUC = 0.97; LR- = 0.001, specificity 100%, p=0.0003), suggesting the importance of infectious risk assessment in SLE patients to ameliorate prevention strategies.

Huang *et al*. (41) analysed incidence rate, risk factors and outcomes of osteomyelitis in SLE and non-SLE patients (matched for age and sex), drawing information from the Taiwanese National Health Insurance database. Osteomyelitis was found in 1,6% of patients with SLE, with an overall incidence rate ratio (IRR) of 8.52 (95% CI 7.24–10.05), and an IRR 41.1 (95% CI 18.57–107.35) in pediatric subgroups. Age >60 years, male gender, malignancy within five years, prior bone fracture and higher daily prednisolone dose increased risk for osteomyelitis.

End-stage renal disease (ESRD) due to lupus nephritis (LN) concerns 10-30% of patients with SLE and can frequently lead to dialysis and/or kidney transplantation (KT).

Clinical outcome of KT for lupus nephritis (LN) seems comparable to other conditions. In a Spanish cohort (42), has not been found a significant differences in graft survival and patient survival between patients with ESRD due to LN (43 patients) and the control group (ESRD due to primary glomerulonephritis, 367 patients). The graft survival rates at 5 and 10 years were 80% and 63% for SLE and 70% and 55% for PGN, respectively. Patient survival at 5 years was 90% in both groups, while, at 10 years, overall survival was 76% in LES and 79% in PGN. There was no recurrence of the disease in any patient. In a Mexican cohort (43) (25 patients with SLE and 50 controls, matched for age, sex, and year of transplantation) survival rates for patients with KT due to LN were lower (66% at 5 years) and 8% of patients experienced a recurrence of LN. Renal graft survival did not differ between patients with SLE and other causes of ESRD.

Take home messages

- Disease activity and therapies are still the major cause of irreversible

organ damage in SLE (37) and, in particular, osteoporosis (38, 39)
- Immunosuppressant therapy, especially cyclophosphamide, and immunological abnormalities are the major risk factors for infections in SLE; a compound clinical-immunological index to predict the occurrence of infections in the short term has been developed end validated (40).

Disease outcomes and treat-to-target

In the last decades, many trials of targeted therapies have been done unsuccessfully and a lack of well-validated endpoints is certainly one of the contributory factors to the recurrent failure of clinical trials in SLE. Recently, the new "treat-to-target" DORIS definition of remission (44) and the LLDAS definition of Lupus Low Disease Activity (45) have been the subjects of multiple validation studies and encouraging data are emerging from large independent cohorts. Importantly, the attainment of these targets seems to be associated with protection from organ damage accrual (46).

Several studies published in the last year have focused on the relationship between the achievement of these targets and disease outcomes: the importance not only of achieving remission/LLDAS but also of maintaining it over time emerges from recent studies.

A study on 558 patients from the LUMINA cohort demonstrated that the longer the percentage of time the patients were in remission/low disease activity, the less damage accrual was observed (rate ratio 0.1773 (95% confidence interval (CI) 0.1216–0.2584) $p<0.0001$). A protective effect on mortality was also observed but was not statistically significant (47). Floris *et al*. compared the effect of LLDAS and clinical remission (CR) in a monocentric cohort of 116 newly diagnosed SLE patients in preventing early damage accrual. LLDAS and CR achievement at 6 months (T1) after treatment initiation and their maintenance over the next 12 months were assessed. Early damage was recorded after 18 months of follow-up (T2) using the SLICC/damage index. They demonstrated that both LLDAS and CR represent valid targets to prevent damage in the early stage of the disease. In particular, they found that CR and LLDAS at T1 were independently associated with lower accrual of early damage. Moreover, patients who steadily persisted in this condition until T2 developed significantly less damage compared to those who failed to maintain it during the T1-T2 interval ($p=0.003$), those who achieved it later than T1 ($p<0.001$) or those who had never been in this condition ($p<0.001$) (48). Remission appears as a desirable outcome in SLE patients but clear guidelines on the management of remitted patients are lacking. In particular, it is still unclear if and when immunosuppressants can be safely withdrawn in SLE patients in durable remission. Zen *et al*. assessed the rate and predictors of flare after immunosuppressant withdrawal in remitted SLE patients. Although the rate of flare was lower in patients who discontinued treatment for remission compared to those who discontinued immunosuppressants due to poor adherence/intolerance, the authors observed that disease flares were not uncommon even in remitted patients after treatment withdrawal, with a flare rate of 24.7%, after a median follow up of 57 months. Importantly, in patients who discontinued immunosuppressants due to remission, maintenance therapy with antimalarials (OR 0.243, 95% CI 0.070, 0.842) and the duration of remission at immunosuppressant discontinuation (OR 0.870, 0.824–0.996) were independent protective factors against disease flare (49).

The LLDAS and DORIS remission definitions were determined *a priori*, based on consensus processes involving multinational expert panels and were subsequently tested in validation studies (46). Given that achieving these conditions seem to be protective for SLE patients, it is important to understand to what extent these targets are achievable in clinical practice and which factors better predict the attainment of these conditions.

Analysing data from the BLISS trials on belimumab, established organ damage at baseline had a negative impact on the attainment of LLDAS. On the contrary, positive anti-dsDNA and a daily prednisone dose ≤7.5 mg were positively associated with the achievement of clinical remission (50).

Interesting data also come from real life data of international cohorts.

In the large SLE cohort of the Johns Hopkins University, recent studies have demonstrated that LLDAS is potentially attainable in the majority of patients, but with greater difficulty in African Americans. In fact, the group by Petri found that a lower percentage of African American patients is able to achieve and maintain the LLDAS condition for ≥50% of the observation time (LLDAS-50). Among 2228 SLE patients, 52.5% of them, but only 37.6% of African Americans, achieved LLDAS-50. A higher percentage of time taking hydroxychloroquine was a modifiable positive predictor of LLDAS-50 (51).

Ugarte *et al*. investigated predictors of remission and low disease activity in a large inception multiethnic Latin American cohort (GLADEL cohort). Of 1480 patients, 902 had an active disease at entry and were followed prospectically. Among them, 196 patients achieved remission (21.7%) and 314 achieved low disease activity (34.8%). Absence of mucocutaneous [HR=1.571 (95%CI 1.064–2.320)], renal [HR=1.487 (95%CI 1.067–2.073)], and haematologic [HR=1.354 (95%CI 1.005–1.825)] involvement, use of immunosuppressive drugs [HR=1.468 (95%CI 1.025–2.105)], and lower disease activity early in the course of the disease [HR=1.028 (95%CI 1.006–1.051) per 1 unit decrease] were predictive of remission in patients with SLE (52). Such data have practical applicability and may guide physicians in determining which patients may benefit from more intensive control of disease activity, always trying to do so without escalation of glucocorticoids, which independently contribute to damage accrual risk in SLE.

In this regard, an interesting study by Ruiz-Irastorza *et al*. demonstrated that prolonged remission on treatment is an achievable target in SLE patients, even by using therapeutic regimens consisting of lower doses of oral prednisone and maximising the use of pulse me-

thyl-prednisolone, hydroxychloroquine and methotrexate. In this study, the authors compared inception patients from two European SLE cohorts (the Cruces Lupus Cohort [CC] and the Bordeaux Lupus Cohort [BC]), with similar clinical presentation and no differences in the mean SLEDAI score at diagnosis. In detail, as far as the glucocorticoid regimen is concerned, patients from CC were treated more frequently with pulse methyl-prednisolone (42% *vs*. 26%), and received lower doses of oral prednisone (average dose during the follow-up 2.3 *vs*. 7.2 mg/d, $p<0.001$) and they demonstrated to be more likely to achieve the target of clinical remission on treatment at one year (84% *vs*. 43%, $p<0.001$) and to maintain prolonged remission during the 5 years of follow up (70% *vs*. 28%, $p<0.001$) (53).

It is important to evaluate the impact of remission/low disease activity on HRQoL, considering that the optimisation of HRQoL in SLE patients is defined as one of the treatment goals in the 2019 EULAR recommendations for the management of SLE (54). To date, only few longitudinal studies investigated the relationship between disease targets and HRQoL. Moreover, available studies are often difficult to compare due to the heterogeneity of the cohorts, the different definitions of remission/low disease activity used, and the different Patient Reported Outcomes adopted to assess HRQoL.

Data from the literature suggest that the relationship between disease activity and QoL is controversial. Nevertheless, overall recent data indicate that the attainment of disease targets may improve patients' perception of health status.

According to recent studies, remission and low disease activity (LDAS) seem to be associated with a better HRQoL, particularly when disease status is maintained for a prolonged period.

Ugarte et al. evaluated longitudinally the impact of LDAS/remission on HRQoL over time, in a Peruvian cohort of 243 SLE patients. They used a disease-specific questionnaire (LupusQoL) and they found that being on LDAS/Remission predicted a better HRQoL, especially in the components of physical health, pain, planning, burden to others, emotional health and fatigue (55).

In the last year, the relationship between remission and HRQoL (measured by the SF-36) was evaluated in a Dutch cohort. Data from 154 patients, mainly female and Caucasian, with 2 years of follow-up were analysed. Remission at baseline was present in 39% of patients. Patients in remission at baseline had higher physical component summary (PCS) compared with patients not in remission (mean 41.5 *vs*. mean 35.4, respectively, $p=0.001$). Moreover, patients in remission on therapy had higher PCS than patients not in remission, and patients in remission off therapy had higher PCS than patients in remission on therapy. No correlation emerged between mental component summary (MCS) and the condition of remission. Interestingly, both patients in prolonged remission and patients never in remission had a significant increase in PCS (mean increase 3.3, $p=0.013$, and 3.7, $p=0.021$, respectively). These data suggest that although a strong association exists between the condition of remission and HRQoL, in particular with the physical component, other factors not directly related to SLE and the level of disease activity may influence patients' perception of health status (56).

A recent study conducted in the multiethnic US LUMINA cohort showed that the duration of remission/low disease activity is associated with better QoL, after adjusting for potential confounders. In a large group of 483 SLE patients, it was demonstrated that per each increase of 10% of the time on remission/LDAS the PCS increased 0.95 and the MCS 0.59. Anyway, these data are difficult to compare with data from other cohorts. In particular, patients included in this study are multiethnic, have a short disease duration (1.4 years) and the authors used definitions of remission/low disease activity that did not allow a stable therapy with immunosuppressants (57). In conclusion, the path towards the ideal treatment target for SLE is perhaps still long but these recent data give encouraging results, showing that the definitions of remission/low disease activity currently in use seem to be achievable targets in clinical practice, with a beneficial effect on clinical outcomes and patients' quality of life.

Take home messages

- Low disease activity (LLDAS) and remission represent valid targets to prevent damage, also in the early stage of the disease (47, 48)
- A treatment with antimalarials and a longer duration of remission at immunosuppressant discontinuation are independent protective factors against disease flare (49)
- Absence of mucocutaneous renal and hematologic involvement, use of immunosuppressive drugs and lower disease activity in the early phases of the disease are predictors of remission attainment (52)
- Remission and LDAS, especially if prolonged, seem to be associated with a better HRQoL, particularly in the physical components (55-57).

Therapies and treatment strategies

As regards treatment, last year, several studies based on real-life experience in SLE were published and new strategies were discussed. Importantly, EULAR published an update to a set of recommendations for the management of systemic lupus erythematosus (54).

To date, glucocorticoids (GCs) are still a cornerstone in SLE treatment, but it would be advisable, whenever possible, to taper and eventually withdraw their assumption. An Italian study on 148 SLE patients showed that after a long-term remission or LLDAS, GCs tapering and complete withdrawal is possible and can also be maintained (58). In a study on 148 Indian patients with clinically remitted SLE (59), GCs and other immunosuppressive agents were tapered with a recurrence rate of 20.9% after a median of 400 days of follow-up. Most of the flares occurred in the first year of follow-up, and 93.5% of flares occurred in patients who received ≤ 8 years of glucocorticoids.

It is well recognised that hydroxychloroquine (HCQ) is effective in SLE. A large study, that compares the outcomes of SLE patients on HCQ with those of SLE patients who discontin-

ued HCQ, was recently published (60). In this retrospective study on over 500 SLE patients, HCQ discontinuation was associated with a greater risk for flares, especially if discontinued after less than a year and from patients with articular and haematological involvement. HCQ is also recommended in pregnancy and is associated with better pregnancy outcomes. In a recent retrospective cohort study of 151 pregnancies in 122 SLE patients (61) the incidence of preeclampsia was significantly lower in the HCQ treatment group than in the HCQ non-treatment group (7.5% *vs*. 19.7%, p=0.032).

Traditional immunosuppressive drugs

Different therapeutic strategies have been proposed for patients with lupus nephritis (LN).

A study on 222 Indian SLE patients with biopsy-proven active LN compared efficacy and safety of four different treatment protocols: low-dose cyclophosphamide (CYC) (total dose = 3 g), high-dose CYC (mean total dose = 5.1 g), mycophenolate (MMF), and Rituximab (RTX). In this cohort high-dose CYC and RTX were associated with better clinical efficacy, with a renal response of 90.3% and 90.9%, respectively. RTX treatment was effective also in relapsing disease course (62).

Another study showed that low-dose leflunomide, in combination with prednisone, had substantially the same effectiveness and safety of CYC and prednisone in the induction therapy of proliferative LN (63). 48 patients received oral leflunomide, with a loading dose of 40 mg/day for 3 days followed by 20 mg/day, while 52 patients received 0.8–1.0 g of intravenous CYC monthly. After 24 weeks, there were no statistically significant differences between the two groups in complete remission rate (23% *vs*. 27%), partial remission rate (56% *vs*. 42%) and clinical parameters.

Adding oral immunosuppressive drugs to intravenous CYC seems to be more effective than using CYC alone, as discussed in a study on 191 LN patients (64). After 24 weeks, the rate of complete remission and total response was higher in the group that was taking CYC, HCQ and an oral immunosuppressant agent (MMF, AZA or leflunomide) compared with the group treated with intravenous CYC alone.

A retrospective analysis of data from 63 patients enrolled in ALMS and AURA trials explored the differences between a high dose and a low dose treatment regimen of MMF and steroids on LN outcomes (65); the lower dose regimen showed better long-term safety without compromising efficacy.

A recent multicentre retrospective observational study (66) evaluated the response to combination therapy (MMF and tacrolimus (TAC)) in 62 patients with LN, refractory to monotherapy either with MMF or TAC. An initial response (reduction in proteinuria and lupus disease activity score) was observed after 3 months, and complete remission was achieved in 22.6% of patients at 6 months and in 36.4% at 1 year. The overall response rate was 56.5% after 6 months and 69.1% after 1 year, with a favourable adverse-event profile.

Rituximab

RTX is used off-label in relapsing and refractory SLE cases. Interesting data emerged from some of the real-life experience studies published last year.

For example, RTX efficacy and safety in SLE was assessed with a retrospective collection of data from four referral centres, with special attention for a subgroup of 80 patients re-treated with RTX as a maintenance agent (67). After 6 months, treatment failure was observed in 27% of the 147 patients. Low C4 and/or lower number of previous immunosuppressive drugs were associated with a better response. In patients re-treated with RTX, active articular disease at the time of the first course of RTX was significantly associated with the risk of flare during the second RTX course (p=0.010), and relapse free survival was similar to that observed in patients treated with a single RTX course.

Another study (68) on 144 SLE patients treated with RTX showed that those with a lower BILAG score at baseline are less likely to benefit from RTX treatment, in contrast to patients with higher BILAG score (p<0.001). Furthermore, treatment failure was significantly lower in patients with renal involvement than in those without it (p=0.021).

Belimumab

Belimumab is indicated as an add-on treatment for adult patients with active, autoantibody-positive SLE. The results of a phase 3, multicentre, double-blind, placebo-controlled, 52-week study (69) suggested that efficacy and safety of intravenous belimumab in SLE Japanese patients are similar to those observed in the overall phase 3 trial population. Of the 707 patients randomised to treatment in the overall trial, 60 patients were enrolled and randomised to belimumab plus standard of care or placebo plus standard of care. In this cohort more patients achieved an SRI4 response at week 52 in the belimumab group compared to the placebo group (46.2% *vs*. 25.0%), and cumulative prednisone use over the treatment period was significantly lower in patients receiving belimumab. Also organ system improvements, assessed by SELENA-SLEDAI and BILAG, were higher in the group treated with belimumab (70), especially for the mucocutaneous domain, while there was a worsening in SELENA-SLEDAI haematologic and renal systems.

Others

In critical patients with severe manifestations of SLE, therapeutic plasma exchange (TPE) could be considered as an option. A retrospective study (71) analysed outcomes and complications in 40 patients with SLE. The main indications for TPE were diffuse alveolar haemorrhage (DAH; n=11) and neurolupus (n=9); although these were selected cases, the procedure was safe and effective.

Another option is intravenous immunoglobulin (IVIG) therapy, usually reserved for severe and refractory SLE cases. IVIG can be considered if conventional therapies are contraindicated and the administration remains off label. In Nieto-Aristizábal *et al*. (72) study, sixty-three SLE patients were treated with at least one IVIG cycle. SLEDAI-2K scores significantly ame-

liorate when the indications were immune thrombocytopenia (10/14 patients with good response) and hypogammaglobulinaemia (8/12 patients).

Thus, in the last year, new data emerged from real life studies focused on treatment optimisation and combination of different strategies; the release of the update EULAR recommendations represents the most important contribution summarising the most recent evidence on this topic.

Take home messages

- While tapering and GC withdrawal can be safe in patients in remission (58, 59), HCQ discontinuation is associated with a risk for flares, in patients with articular and haematological involvement (60)
- Data on combination therapy show promising results in lupus nephritis (*i.e.* CYC+ RTX: MMF+ TAC) (62-66)
- Confirmatory data show that Belimumab is effective in different ethnicities (69-70), and Rituximab can have a role in subgroups of patients with higher disease activity and as a maintenance therapy in lupus nephritis (67-70).

Conclusions

In 2019, many interesting papers were published on SLE, indicating the growing interest in this complex disease. In this review, we tried to summarise the most relevant findings, including new insights into disease pathogenesis, new diagnostic tools, and new treatment strategies for SLE.

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