Review

One year in review 2019: systemic lupus erythematosus

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Received on June 19, 2019; accepted in revised form on July 1, 2019.

Clin Exp Rheumatol 2019; 37: 715-722.

Key words: systemic lupus erythematosus, pathogenesis, comorbidities, treatment

Competing interests: none declared.

ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune connective-tissue disorder with a wide range of clinical manifestations that predominantly affect women. Many aspects of its pathogenesis are still unclear, and new therapeutic strategies are progressively emerging. Thus, in this review we aim to summarise the most relevant data on SLE that emerged during 2018, following the previous annual review of this series. In particular, the review will focus on new insights in SLE regarding new pathogenetic pathways, new biomarkers, new data on clinical manifestations, clinical outcomes and comorbidities and what has emerged on new drugs and new therapeutic strategies.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease with extremely varied clinical manifestations and a complex pathogenesis.

We performed a Medline search of English language articles published from 1st January to 31st December 2018 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 and selected the most relevant papers, excluding reviews and considering only papers on adult SLE. The aim of this review is to describe the most relevant data about SLE emerged during 2018, following the previous *One Year in Review* of this series (1).

Pathogenesis and new therapeutic approaches

Innate and adaptive immunity

Evidence supports a strong association between SLE and complement C1q deficiency. A recent study (2) has highlighted the role of C1q in suppressing the activation and expansion of $CD8^+$ T cells in an SLE model, revealing a new function of this molecule in addition to its role of complement activation. C1q restrained the response to self-antigens by modulating the mitochondrial metabolism of $CD8^+$ T cells and its deficiency triggered an exuberant $CD8^+$ T cell response to chronic viral infection with implications in the perpetuation of autoimmunity.

Autoreactive B and T cells clearly play a pathogenic role in autoimmunity and SLE. B cells are generated with the help of a distinct subset of $CD4^+$ T cells, called T follicular helper (Tfh) cells, within a specialised microenvironment known as the germinal centre. Beccaria *et al*. (3) analysed the role of Galectin-3 in germinal centre development, a process based on delicate crosstalk between B and T cell populations. In this study, the absence of Galectin-3 in mice caused an excess of IFN-γ, which raised aberrant germinal centre formation and autoantibody production.

Even if the production of autoantibodies in SLE patients is interrelated to dysregulated Tfh differentiation, it is unclear how immunopathologic Tfh compartment is replenished continuously. Stem cell-like memory T cells are likely to be the cellular source of differentiated Tfh cells in SLE patients (4). Is not clear which factors trigger Tfh response and germinal centre reaction. A role for cytokine IL-27 was suggested since Ryu and co-workers (5) reported that in a mouse model of SLE, the atherogenic environment induced the release of IL-27 from dendritic cells in a Toll-like receptor (TLR) 4-dependent manner and that blockade of this pathway decreased Tfh cell responses. In any case, high glucose utilisation appears to be a unique requirement of autoreactive Tfh (6) since in lupus-prone models inhibition of glycolysis reduce the expansion of autoreactive Tfh cells.

Recently, a small subset of B cells co-

expressing two different chains heavy or light Ig and, thus, two dual-antibody autoreactive BCRs (B_{2R} cells) has been specifically implicated in SLE pathogenesis. Sang *et al*. (7) demonstrated that T cell-dependent signals and innate stimuli, such as IL-21, type I and II interferon (INF), and TLR 7-9 agonists, played a key role in the activation, expansion, and effector function of B_{2R} cells in the MRL/lpr mouse model of lupus. In the same model, in addition to secreting antibodies, B_{2R} cells expressed much higher levels of MHCII and additional surface receptors important for cognate engagement with T cells. Among these co-receptors, the authors have demonstrated that deficiency in IL-21R (stimulated by IL-21, a T cell-derived soluble factor implicated in the generation of germinal centre B cells and Ig class-switched plasma cells) reduced the frequency of B_{2R} cells, indicating their enhanced dependency on IL-21 for the maturation.

Another population of B cells studied in SLE is a B cell subset that expresses CD11c, called T-bet$^+$ B cells, which are antigen-experienced cells. Wang *et al*. (8) demonstrated that these cells were expanded in a cohort of over 200 SLE patients, and the degree of expansion correlated with disease activity. Moreover, IL-21 potently induced T-bet$^+$ B cells promoting their differentiation into Ig-secreting autoreactive plasma cells.

The growing importance in IL-21 as a pathogenetic factor implicated in SLE is proved by its role in the blockade of Treg cell autophagy, differentiation, and function through the activation of mTOR complexes 1 and 2 (9). In the same study, 4-week of rapamycin treatment reverted these effects inducing autophagy and restoring Treg cells function.

Finally, in the past year, new evidence emerged on the mechanism of action of B cell activating factor (BAFF), suggesting new strategies to either activate or inhibit BAFF activity. In humans, BAFF exists in both a membrane-bound form and two soluble forms as a trimer or 60-mer. In order to form BAFF 60-mer, trimer forms interact via a loop region of 10 amino acid residues called the flap. Vigolo *et al*. (10) demonstrated that a loop region of BAFF controlled B cell survival and regulated recognition by different inhibitors. The authors described that the flap was essential for the activity of soluble BAFF trimers acting on BAFF receptor. In addition, their experiments strongly suggested that BAFF inhibitors belimumab and atacicept differ in their mechanism of BAFF 60-mer inhibition because belimumab, unlike atacicept, did not (immediately) inhibit BAFF 60-mer.

Genetic and epigenetic factors

Genetic studies have identified more than 80 loci associated with increased susceptibility to SLE, and one of the strongest SLE risk loci is the signal transducer and activator of transcription (STAT)4. It is involved in inflammatory response following IL-12 receptor stimulation and in the non-canonical signalling pathway of the type I IFN receptor. A study conducted in a cohort of 52 genotyped patients with SLE established that a genetic variant in STAT4 (rs7574865[T]) which is known to be associated with strong SLE risk augmented responsiveness to IL-12 and increased IF IFN-γ production in T cells. Therefore, this variant might be a potential target for inhibitors of the JAK-STA pathway (11). In addition, a recent report suggested that IL-12-mediated co-activation of STAT1 and STAT4 altered histone modification, with sequentially expansion of Tfh-Th1-like cells. The findings of these epigenetic modifications resulted in the induction of pathogenic Tfh cells, and it could be potentially helpful towards the development of cell-specific and effective treatment for SLE (12). Epigenetic regulation is emerging as an important contributing factor in SLE, too. A large comprehensive study (13) generated genome-wide methylation profiles from a large collection of patients with SLE and healthy controls. The largest methylation differences were observed at type I interferon (IFN)-regulated genes which exhibited decreased methylation in SLE. In addition, associations with a large fraction of differentially methylated CpGs were reported. For example, several differentially methylated CpGs were found at the PDCD1 gene, which is a known SLE susceptibility locus implicated in the inhibition of self-reactive lymphocytic activation or in the X-chromosome by independently analysing females and males. Tsuo *et al*. (14) demonstrated that EZH2, an epigenetic regulator that modulates DNA methylation, had an increased expression in naive CD4$^+$ T cells obtained from SLE patients and altered the DNA methylome promoting leukocyte adhesion and migration.

Biomarkers

In the last year, several studies have been published about new emerging biomarkers that have been correlated with systemic disease activity, organ involvement and treatment response.

A recent study demonstrated the possible important role of Collagen triple helix repeat containing-1 (CTHRC1) as marker of active disease. In particular it has been observed that serum CTHRC1 levels correlate with SLEDAI and its serum level was higher in SLE patients with arthritis and anaemia compared with patients without these manifestations (15).

Considering the importance of regulatory T cells in maintaining immune self-tolerance, a Chinese study found that in SLE, approximately 3% of CD4$^+$ T cells expressed Foxp3, the signature transcription factor of Treg cells, but did not express CD25 with a phenotype of CD4$^+$CD25-Foxp3$^+$. This cell subset seems to have a significantly positive correlation with systemic disease activity or anti-dsDNA titre; moreover CD4$^+$CD25-Foxp3$^+$ T cells were significantly increased in patients with skin, haematological and articular involvement (16). Other news come from two Korean studies of Ahn *et al*. (17, 18): the first tried to evaluate the clinical significance of serum aminoacyl-tRNA synthetase-interacting multifunctional protein-1 (AIMP1); the second one evaluated whether serum leucine-rich α2-glicoprotein (LRG) is associated with disease activity in SLE patients. In both studies the results showed a positive correlation between two serum markers (AIMP1 and LRG) and disease activity; moreover, both AIMP1 and LRG could be useful for predicting active SLE. Also the level of circulating

cell-free DNA (cDNA) could represent a useful marker: in fact, compared to control group, the median levels of cDNA were higher in SLE patients, and in particular in those patients with active disease (19).

An interesting study investigated the possible role of serum level of the IFN-regulated cytochine CXCL13 (20). It has been observed that CXCL13 correlated with disease activity but not in cases of cutaneous SLE (subacute or chronic cutaneous lupus). Moreover, the study suggested that when levels of CXCL13 were high, it was more likely the evolution to SLE. The study by Ribeiro *et al*. (21) confirmed that CXCL13 was related to disease activity but it was not associated to articular involvement.

As far as biomarkers of specific organ involvement are concerned, a recent study (22) observed that urinary BAFF (uBAFF) was detectable in SLE patients but not in patients with primary Sjögren's syndrome, or immunoglobulin IgA nephropathy, or healthy controls; among SLE patients, uBAFF was higher in those with active renal disease (p=0.02). These results suggested a possible role of this molecule as marker of renal disease activity in SLE.

Other promising urinary biomarkers are kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and monocyte chemoattractant protein-1 (MCP-1). A Chinese study demonstrated that urinary levels of these three proteins were higher in patients with active LN compared with patients with LN in remission and normal controls (p<0.001), and the combination of KIM-1 and NGAL seems to be an independent risk factor for renal outcomes (23).

Another study measured serum and urine levels of IFN-Y, CXCL16 and uPAR in 50 SLE patients with and without lupus nephritis (LN) and 15 healthy controls: it has been observed that the urine and serum levels of these markers were higher in SLE patients and among SLE patients, they were increased in LN patients. Finally, the expression of these biomarkers in renal tissue was associated with the activity of pathological lesions (24).

Similar results were obtained by investigating a role of anti-α enolase antibodies. Li *et al*. (25) measured serum levels of these antibodies in SLE patients and they observed that it was higher in SLE patients and, in particular, in the presence of LN; the level of these antibodies seems to correlate with serum whole IgG and 24-hour urine protein.

The level of plasma cysteine rich 61 (Cyr61), obtained from 54 patients with SLE and associated pulmonary arterial hypertension (PAH), was higher in SLE-PAH than in SLE-non-PAH (n=52) and healthy controls (n=54) (26), so it seems to be a promising biomarker to identify PAH in SLE and a prognosis indicator.

For neuropsychiatric involvement (NP-SLE), Noris-Garcia *et al*. (27) evaluated serum levels of S100B. This protein belongs to a family of calcium-binding proteins and it is implicated with several psychiatric or neurologic disorders. S100B has been evaluated in 47 SLE patients and in 20 healthy controls showing that that serum S100B was significantly higher in SLE patients and, in particular, in patients with neuropsychiatric involvement suggesting a possible role as biomarker for NPSLE.

Another study identified a positive correlation between blood-brain barrier damages (evaluated by Q albumin) in NPSLE and anti-Sm (p=0.0040), while anti-NR2, anti-P and anti-cardiolipin were not significantly correlated with blood-brain barrier dysfunction (28).

As far as joint involvement is concerned, a recent study observed an association between anti- carbamylated proteins antibodies (anti-CarP) and erosive damage also in SLE-related arthritis (29).

Clinical manifestations

Over the last few years, joint involvement in SLE raised great interest and one of the main reasons is the widespread application of imaging techniques to assess it (30).

Di Matteo *et al*. (31) found a very high prevalence of ultrasonography (US) abnormalities in consecutive SLE patients with current or previous joint symptoms (35% of the scanned joints, 32.6% of the scanned tendons and in 24.4% of the scanned entheses (24.4%). Furthermore, a broad spectrum of US changes also involving anatomic structures not considered in previous investigations including entheses and tendons with no synovial sheath, was detected (32).

Through a cross-sectional multicentre study, 151 consecutive adult SLE patients were recruited and studied by a clinical standardised joint assessment, B-mode and Power Doppler (PD) US of 40 joints and 26 tendons. Confirming the results for the enthesis described in the former study, the authors observed a high frequency of subclinical US abnormalities in asymptomatic patients: 85% of patients without joint symptoms had at least 1 US abnormality. The most frequent abnormalities described were joint effusions, synovial hypertrophy and synovitis. Joint or tendon PD signal (grade>1) was found in 44% of patients (33).

Recent interesting data have been published on cardiovascular (CV) involvement in SLE.

Thilo Burkard *et al*. assessed the prevalence of subclinical heart disease in SLE by performing CV magnetic resonance (MR) in patients without known CV disease. CVMR was abnormal in 13 of the 30 enrolled patients (43%), showing late gadolinium enhancement (LGE) in 9/13, stress perfusion deficits in 5/13 and pericardial effusion (PE) in 7/13. No correlation was found between clinical symptoms and CVMR results (34).

Consistent with these results, 80 SLE patients with atypical cardiac symptoms/signs (fatigue, mild shortness of breath, early repolarisation and sinus tachycardia) with normal echocardiography, were evaluated using MR (35). Abnormal CVMR findings were identified in 22/80 (27.5%) of SLE patients, including 4/22 with recent silent myocarditis, 5/22 with past myocarditis, 9/22 with past myocardial infarction and 4/22 with diffuse subendocardial fibrosis due to vasculitis; again, it was demonstrated that MR in SLE patients with atypical cardiac symptoms/signs and normal echocardiography can assess occult cardiac lesions.

With regard to renal involvement, Moroni *et al*. published a pivotal study

last year (36). The authors evaluated changes in demographic, clinical and histological presentation, and prognosis of LN over time in a multicentre cohort of 499 patients diagnosed with LN from 1970 to 2016. They found that clinical presentation of LN has become less severe in the last years, leading to a better long-term renal survival. During this study the 46-year follow-up was subdivided into three periods (P): P1 1970-1985, P2 1986-2001 and P3 2002-2016, and patients accordingly grouped based on the year of LN diagnosis. The frequency of renal insufficiency at the time of LN presentation progressively decreased while the presentation with isolated urinary abnormalities was more frequent over time. No changes in histological class and activity index were observed, while chronicity index significantly decreased from 1970 to 2016 (p=0.023). Survival without end-stage renal disease (ESRD) was 87% in P1, 94% in P2% and 99% in P3 at 10 years, 80% in P1 and 90% in P2 at 20 years. Furthermore male gender, arterial hypertension, absence of maintenance immunosuppressive therapy, increased serum creatinine, and high activity and chronicity index were independent predictors of ESRD.

The presence of tubulointerstitial damage (TID) on renal biopsy is considered to be a late sequela of LN. From the retrospective data from a population of 131 patients with biopsy proven LN, Broder *et al*. showed that moderate-to-severe TID, but not tubulointerstitial inflammation, was a strong predictor of ESRD progression independent of estimated glomerular filtration rate (eGFR) or glomerular findings (37).

In the neuropsychiatric field, one of the most interesting study was by Papadaki *et al*. (38); 76 patients with SLE (37 primary NPSLE, 16 secondary NPSLE, 23 non-NPSLE) and 31 healthy controls underwent conventional MR (cMR) and dynamic susceptibility contrast enhanced perfusion MR (DSC-MR), a minimally invasive method of cerebral perfusion assessment. The authors observed that primary NPSLE was characterised by significant hypoperfusion in cerebral white matter that appears normal on cMR. Moreover, they concluded that the combination of DSC-MRI-measured blood flow in the brain semioval centre with conventional MR could be useful in ameliorating diagnostic accuracy of NPSLE. A cut-off for cerebral blood flow of 0.77 in the left semioval centre discriminated primary NPSLE from non-NPSLE/secondary NPSLE with 80% sensitivity and 67–69% specificity. Blood flow values in the left semioval centre showed substantially higher sensitivity than cMR (81% *vs*. 19–24%) for diagnosing primary NPSLE with the combination of the two modalities yielding 94–100% specificity in discriminating primary from secondary NPSLE.

Comorbidities

Comorbidities substantially contribute to the disease burden in patients with SLE; a study from UK primary care in a population of 1605 incident cases of SLE and 6284 matched controls showed that SLE is associated with a greater risk of several comorbidities both at diagnosis and post-diagnosis; furthermore, comorbidities at SLE diagnosis accounted for 27.6% of the apparent difference in mortality between SLE patients and matched controls (39).

In another study, African Americans with SLE were found to have more comorbidities in every organ system and the most striking were hypertension (OR=4.25), renal dialysis (OR=10.90), and pneumonia (OR=3.57) (40).

Several studies have been published on specific comorbidities, we selected the most relevant focusing on CV, psychological and musculoskeletal complications.

Metabolic and cardiovascular comorbidities

Despite the well recognised importance of CV comorbidities, an appropriate risk assessment in SLE patients is sometimes inadequate as demonstrated by the survey among 91 members of the Canadian Rheumatology Association (41). Indeed, almost all responders (91%) believed that SLE is a major CV risk factor, and 68% felt rheumatologists should assess CV risk; however, 42% declared not to be familiar with recommendations on CV risk management.

Among CV risk factors, metabolic syndrome (MetS) is an emerging issue in SLE patients; in a recent study the effect of MetS on organ damage and mortality in a population of 577 SLE patients was evaluated; patients with MetS had significantly more damage accrual over time, an increased risk of vascular events (11% *vs*. 2.8%), all-cause (14% *vs*. 5.5%) and vascular (7.1% *vs*. 0.2%) mortality (42).

Recently, a study on 453 SLE patients treated with antimalarial (AM) was performed to investigate the role of this therapy in determining ECG abnormalities (43). The results showed that cumulative AM dose above the median (1207 g) was associated with decreased odds of ECG conduction abnormalities, while there was borderline statistical significance for the association with left ventricular hypertrophy or atrial enlargement.

Psychological disorders

Psychopathological comorbidities are a major issue in patients with SLE with a significant impact on patient's quality of life; in particular, a recent study showed that young adults with childhood-onset have a higher risk of major depression episodes (OR 1.7) and recurrent episodes (OR 2.2) compared to those with adult-onset SLE (44).

A Korean study on 505 SLE patients identified smoking status, organ damage and antiphospholipid antibodies as risk factors for depression while high-level education and a high income were protective factors (45).

In a cross-sectional study on 202 women with SLE and 223 healthy women, also disease duration, disease activity, cumulative organ damage, and perceived stress resulted significant predictors of psychopathological manifestations (46).

A recent study investigated the interplay between physical and psychiatric manifestations of SLE in 72 patients that were evaluated for psychological status, clinical profiles and laboratory test values (47). The prevalence of depression in this cohort was 41.7%; was described that pain, body mass index, Chalder's fatigue scale, fatigue severity scale, and anxiety were positively correlated with depression, as were also

complaint alopecia and relationship assessment scale scores. However, the best indicators directly correlated with depression for the SLE cohort where identified in fatigue severity scale, SF-36 physical function, physical role function, and mental health.

Musculoskeletal comorbidities

As far as musculoskeletal comorbidities are concerned, in the Toronto lupus Cohort a prevalence of 13.5% of symptomatic avascular necrosis (AVN) is reported; hips and knees were most commonly affected and 47% of the patients had multiple sites involve; Glucocorticoid (GC) treatment was confirmed as the primary predictor for the development of AVN (48).

Similarly, in a Korean population of 1219 SLE patients, symptomatic AVN was found to be the most common type of musculoskeletal damage (10.8%, n=132) (49). The cumulative GC dose greater than 20 g (OR 3.62,) and use of immunosuppressants including cyclophosphamide or mycophenolate mofetil (MMF) (OR 4.51) were significant independent risk factors for AVN.

Mortality, damage, remission, low disease activity

In a population-based cohort study a comparison was made between an early cohort of 1470 patients (diagnosed between 1999–2006) and a late cohort of 1666 patients (diagnosed between 2007-2014) (50). Interestingly, in both cohorts, the excess mortality compared with healthy matched comparators was similar (15.9 *vs*. 7.9 deaths/1000 person-years in the early cohort and 13.8 *vs*. 7.0 deaths/1000 in the late cohort) suggesting that mortality has not improved among SLE patients in recent years, remaining greater than double that of comparators.

Recent data from the UCSF Lupus Outcomes Study (n=728) showed that that both SF36 physical component score and self-rated health were associated with mortality; in particular, lower scores of SF36 Physical Function independently predicted mortality (51).

In the last years, definitions for remission and low disease activity state (LLDAS) have been proposed and their reliability as outcomes measures has been tested. In 2018, prevalence, duration and effect on damage accrual of remission and LLDAS were evaluated in a monocentric cohort of 293 Caucasian patients with SLE during a 7-year follow-up period. Patients who spent at least two consecutive years in LLDAS had significantly less damage accrual with respect to the rest of the cohort, confirming the protective effect of LLDAS on damage accrual (52).

Tselios *et al*. (53) recently described the prevalence of an atypical "monophasic" course of the disease defined as clinical remission achieved within 5 years since enrolment and maintained for ≥10 years of observation; this condition was reported in 7.5% of their cohort. Interestingly, ten years after achieving remission, two-thirds of the patients had discontinued GC; the remaining were treated with 5 mg/day on average.

Therapy

New perspectives on "old" drugs

GCs remain an important approach to SLE therapy, especially for serious organ involvement. Combining different therapies might be a strategy to reduce GC dosages and the related side effects, as described by Ruiz-Arruza *et al*. (54) in a study that compared different treatment options in SLE patients. The results showed that the group (n=74) who received lower GC dosages, more methylprednisolone pulses, earlier immunosuppressive therapy and more hydroxychloroquine (HCQ) presented similar damage caused by SLE but less GCs-related damage and cardiovascular disease if compared to the other group (n=213).

Recently, there has been growing interest in calcineurin inhibitors to treat renal and extra-renal manifestations; new data about real-life experiences with tacrolimus (TAC) was obtained from Asian and European cohorts showing that TAC can be an effective option in LN (55) and in extra-renal manifestations (56) and, especially, haematological manifestations (57). Renal response in SLE patients seems to be good also under cyclosporine (CsA) treatment, as described by Yang *et al*. (58). Up to 25% and 65% of the 60 patients enrolled in this study achieved complete or partial remission, respectively, and no death or progression to ESRD was observed.

A multitargeted therapy with MMF and CsA is another promising strategy in refractory LN (59).

Phase III trials, post-marketing studies and real-life data on biological drugs

Since belimumab was approved, more and more data are being collected about the efficacy and safety of the drug from long-term extension studies and real-life. Furie *et al*. (60) analysed the long-term drug's safety profile in a multicentre, continuation study conducted in 268 patients who completed the 76-week phase III parent study BLISS-76 in the United States. Overall, 54.1% of the entire study population had at least an adverse event (AE) that was considered by the investigator to be drug-related. Discontinuation of belimumab due to an AE occurred in 9.7% of patients with the majority of these occurring in the first 4 years of the study. The most common AEs (occurring in ≥25% of patients) were arthralgia, nausea, headache, upper respiratory tract infections and bacterial urinary tract infection. As far as the long-term efficacy of belimumab, in the present study an overall decrease in disease activity was observed and, in particular, 75.6% of patients achieved an SLE Responder Index (SRI) response at study year 7 midpoint.

In 2018, Zhang *et al*. published the results of a phase III, multicentre, randomised, double-blind, placebo-controlled study conducted in 49 centres across China, Japan and South Korea (61) confirming the efficacy and safety of belimumab in this large Asian SLE population.

As far as real-life is concerned, a large Italian multicentre study was conducted on 188 patients with active SLE treated with belimumab and prospectively followed in 11 referral centres (62) with the specific aim to identify baseline predictors of drug response or discontinuation in clinical practice. In the multivariate analysis, high disease activity (SLEDAI-2K ≥10) and higher GC dosage (prednisone 7.5 mg/day) at base-

line resulted good predictors of SRI-4 response. Moreover, the authors also found a significant decrease in flare rate and in the number of patients having a flare after belimumab initiation compared with the corresponding period before, suggesting a benefit also in patients with a relapsing-remitting disease.

Although rituximab (RTX) is not licensed for SLE, recent studies on real life experiences confirmed that it may be effective as a GC-sparing agent and on reducing disease activity.

Results from BILAG-BR in 270 SLE patients refractory to conventional therapy and treated with biological agents (RTX in 261 of them) showed that almost 50% of them presented improvement in disease activity and reduction in GC use (63). Serris *et al*. (64) published the results of a large multicentre retrospective cohort of patients (n=71) on the efficacy and safety of RTX for treating SLE-associated GC-refractory autoimmune cytopenias. RTX resulted to be effective and relatively safe with an initial response rate up to 86% (complete response in 60.5%) and good results were observed also in case of relapse.

Sequential treatment with RTX and belimumab seems to be an effective option in SLE patients refractory to conventional therapies, as described in a pilot investigation involving three patients (65). Benefits were observed in long standing remission and GC discontinuation.

A safe and effective alternative for B cell-depletion therapy in patients who present severe infusion reactions to RTX, might be ofatumumab, a humanised anti-CD20 monoclonal antibody, as discussed in a single-centre retrospective case series of 16 patients (66). Finally, although the results of EMBODY 1 and EMBODY 2 trials did not confirm the efficacy of epratuzumab (a humanised monoclonal IgG antibody directed against CD22 on B cells) a recent post hoc analysis (67) showed that patients with SLE and associated Sjögren's syndrome presented improvement in SLE disease activity under epratuzumab treatment. In particular, they achieved a BICLA response, a reduction in BILAG total score and a faster reduction of B cell number and IgM level.

Phase I e II studies

A phase Ib, randomised, double-blind, placebo-controlled study showed safety and potential efficacy of AMG 557, a fully human antibody directed against the inducible T cell costimulator ligand (ICOSL) in patients with lupus arthritis. Compared with placebo, patients in the AMG 557 group improved in the global BILAG index scores (-36.3% *vs*. -24.7%), in the SLEDAI score (-47.8% *vs*. -10.7%) and in tender (-22.8% *vs*. -13.5%) and swollen (-62.1% *vs*. -7.8%) joint counts on day 169 (68). Efficacy and safety of ustekinumab, a monoclonal antibody targeting IL-12 and IL-23 was assessed in a multicentre, double-blind, phase 2, randomised, controlled trial of patients with active SLE. At week 24, 62% (37/60) of patients in the ustekinumab group and 33% of (14/42) patients in the placebo group achieved an SRI-4 response (percentage difference 28%, 95%CI 10–47; p=0·006). Infections were the most common type of adverse event in the whole population (45% in the ustekinumab group *versus* 50% in the placebo group) (69). An international, double-blind, randomised, placebo-controlled, phase 2 trial demonstrated that the baricitinib 4 mg dose, but not 2 mg dose, significantly improved the signs and symptoms of patients with active SLE, who were receiving standard background therapy. Serious adverse events were reported in five (5%) patients receiving placebo, 11 (10%) patients receiving baricitinib 2 mg, and ten (10%) patients receiving baricitinib 4 mg. One case of deep-vein thrombosis was reported in a patient with antiphospholipid antibodies in the baricitinib 4 mg group (70).

Emerging potential therapeutic targets

In a phase 1/2 trial, rapamycin, a medication under the generic designation of sirolimus, was assessed in a prospective, biomarker-driven, open-label phase 1/2 clinical trial. SLE patients with active disease activity received oral sirolimus at a starting dose of 2 mg per day, with dose adjusted to maintain a therapeutic range of 6–15 ng/ml. SLEDAI and BILAG disease activity scores were reduced during 12 months of treatment in 16 (55%) of 29 patients who completed treatment, and the mean daily dose of prednisone required to control disease activity decreased from 23.7 mg to 7.2 mg (p<0.001) after 12 months of treatment. Jointly with a progressive improvement in disease activity, sirolimus induced a correction of pro-inflammatory T-cell lineage (expanded $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells and $CD8^+$ memory T-cells) (71). The role of phosphopeptide P140 (Lupuzor, another inhibitor of autophagy currently being evaluated in late-stage clinical trials for the treatment of lupus), on human T and B cells was investigated by Wilhelm *et al*. (72). The authors demonstrated that the peptide down-regulated the maturation and differentiation of B cells into plasma cells, and decreased IgG secretion due to the resulting lack of T cell signalling and activation, thus explaining the highly promising results obtained in clinical trials.

Non-canonical NF-κB signalling seems to be a promising therapeutic target in SLE. Liu *et al*. demonstrated that Peli1, a protein involved in the protein ubiquitination via noncanonical NF-κB signalling dependent on the NF-κB inducing kinase (NIK), acted as a negative regulator on this pathway. In a mouse model of SLE, overexpression of Peli1 inhibited noncanonical NF-κB activation and alleviated lupus-like disease. In humans, PELI1 levels negatively correlated with disease severity (73).

In experimental NZB/W F1 lupus, treatment with a highly selective and potent NIK small molecule led to inhibition of multiple pathways known to be involved in SLE, including OX40 and TWEAK, resulting in an improvement of disease biomarkers (74).

Conclusion

During 2018 many interesting data were published on SLE, indicating the growing interest in this complex disease. Exciting news in several aspects of the disease emerged, including new insights into disease pathogenesis, new diagnostic tools, and new treatment strategies for SLE, which are summarised in this review.

References

1. DI BATTISTA M, MARCUCCI E, ELEFANTE E *et al*.: One year in review 2018: systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 763-77.
2. LING GS, CRAWFORD G, BUANG N *et al*.: C1q restrains autoimmunity and viral infection by regulating $CD8^{(+)}$ T cell metabolism. *Science* 2018; 360: 558-63.
3. BECCARIA CG, AMEZCUA VESELY MC, FIOCCA VERNENGO F *et al*.: Galectin-3 deficiency drives lupus-like disease by promoting spontaneous germinal centers formation via IFN-gamma. *Nat Commun* 2018; 9: 1628.
4. LEE YJ, PARK JA, KWON H *et al*.: Role of Stem Cell-Like Memory T Cells in Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2018; 70: 1459-69.
5. RYU H, LIM H, CHOI G *et al*.: Atherogenic dyslipidemia promotes autoimmune follicular helper T cell responses via IL-27. *Nat Immunol* 2018; 19: 583-93.
6. CHOI SC, TITOV AA, ABBOUD G *et al*.: Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells. *Nat Commun* 2018; 9: 4369.
7. SANG A, DANHORN T, PETERSON JN *et al*.: Innate and adaptive signals enhance differentiation and expansion of dual-antibody autoreactive B cells in lupus. *Nat Commun* 2018; 9: 3973.
8. WANG S, WANG J, KUMAR V *et al*.: IL-21 drives expansion and plasma cell differentiation of autoreactive $CD11c^{(hi)}$T-$bet^{(+)}$ B cells in SLE. *Nat Commun* 2018; 9: 1758.
9. KATO H, PERL A: Blockade of treg cell differentiation and function by the interleukin-21-mechanistic target of rapamycin axis via suppression of autophagy in patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2018; 70: 427-38.
10. VIGOLO M, CHAMBERS MG, WILLEN L *et al*.: A loop region of BAFF controls B cell survival and regulates recognition by different inhibitors. *Nat Commun* 2018; 9: 1199.
11. HAGBERG N, JOELSSON M, LEONARD D *et al*.: The STAT4 SLE risk allele rs7574865[T] is associated with increased IL-12-induced IFN-gamma production in T cells from patients with SLE. *Ann Rheum Dis* 2018; 77: 1070-7.
12. MA X, NAKAYAMADA S, KUBO S *et al*.: Expansion of T follicular helper-T helper 1 like cells through epigenetic regulation by signal transducer and activator of transcription factors. *Ann Rheum Dis* 2018; 77: 1354-61.
13. IMGENBERG-KREUZ J, CARLSSON ALMLOF J, LEONARD D *et al*.: DNA methylation mapping identifies gene regulatory effects in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2018; 77: 736-43.
14. TSOU PS, COIT P, KILIAN NC, SAWALHA AH: EZH2 modulates the DNA methylome and controls T cell adhesion through junctional adhesion molecule A in lupus patients. *Arthritis Rheumatol* 2018; 70: 98-108.
15. WU Q, YANG Q, SUN H: Collagen triple helix repeat containing-1: a novel biomarker associated with disease activity in systemic lupus erythematosus. *Lupus* 2018; 27: 2076-85.
16. YIN ZJ, JU BM, ZHU L *et al*.: Increased $CD4^{(+)}$ $CD25^{(-)}$$Foxp3^{(+)}$ T cells in Chinese systemic lupus erythematosus: correlate with disease activity and organ involvement. *Lupus* 2018; 27: 2057-68.
17. AHN SS, HONG SH, PARK Y *et al*.: Serum aminoacyl-tRNA synthetase-interacting multifunctional protein-1 (AIMP1), a novel disease activity predictive biomarker of systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 533-9.
18. AHN SS, PARK Y, JUNG SM, SONG JJ, PARK YB, LEE SW: Serum leucine-rich alpha2-glycoprotein is elevated in patients with systemic lupus erythematosus and correlates with disease activity. *Clin Chim Acta* 2018; 486: 253-8.
19. XU Y, SONG Y, CHANG J *et al*.: High levels of circulating cell-free DNA are a biomarker of active SLE. *Eur J Clin Invest* 2018; 48: e13015.
20. NIEDERKORN A, FRUHAUF J, SCHWANTZER G *et al*.: CXCL13 is an activity marker for systemic, but not cutaneous lupus erythematosus: a longitudinal cohort study. *Arch Dermatol Res* 2018; 310: 485-93.
21. RIBEIRO DS, LINS CF, GALVAO V *et al*.: Association of CXCL13 serum level and ultrasonographic findings of joints in patients with systemic lupus erythematosus and Jaccoud's arthropathy. *Lupus* 2018; 27: 939-46.
22. VINCENT FB, KANDANE-RATHNAYAKE R, HOI AY *et al*.: Urinary B-cell-activating factor of the tumour necrosis factor family (BAFF) in systemic lupus erythematosus. *Lupus* 2018; 27: 2029-40.
23. DING Y, NIE LM, PANG Y *et al*.: Composite urinary biomarkers to predict pathological tubulointerstitial lesions in lupus nephritis. *Lupus* 2018; 27: 1778-89.
24. WEN S, HE F, ZHU X, YUAN S, LIU H, SUN L: IFN-gamma, CXCL16, uPAR: potential biomarkers for systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 36-43.
25. LI M, LI J, WANG J, LI Y, YANG P: Serum level of anti-alpha-enolase antibody in untreated systemic lupus erythematosus patients correlates with 24-hour urine protein and D-dimer. *Lupus* 2018; 27: 139-42.
26. FAN Y, ZHAO J, QIAN J *et al*.: Cysteine-rich protein 61 as a novel biomarker in systemic lupus erythematosus-associated pulmonary arterial hypertension. *Clin Exp Rheumatol* 2019; 37: 623-32.
27. NORIS-GARCIA E, ARCE S, NARDIN P *et al*.: Peripheral levels of brain-derived neurotrophic factor and S100B in neuropsychiatric systemic lupus erythematous. *Lupus* 2018; 27: 2041-9.
28. HIROHATA S, SAKUMA Y, MATSUEDA Y, ARINUMA Y, YANAGIDA T: Role of serum autoantibodies in blood brain barrier damages in neuropsychiatric systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 1003-7.
29. CECCARELLI F, PERRICONE C, COLASANTI T *et al*.: Anti-carbamylated protein antibodies as a new biomarker of erosive joint damage in systemic lupus erythematosus. *Arthritis Res Ther* 2018; 20: 126.
30. TANI C, CARLI L, STAGNARO C *et al*.: Imaging of joints in systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36 (Suppl. 114): S68-73.
31. DI MATTEO A, DE ANGELIS R, CIPOLLETTA E, FILIPPUCCI E, GRASSI W: Systemic lupus erythematosus arthropathy: the sonographic perspective. *Lupus* 2018; 27: 794-801.
32. DI MATTEO A, FILIPPUCCI E, CIPOLLETTA E *et al*.: Entheseal involvement in patients with systemic lupus erythematosus: an ultrasound study. *Rheumatology* 2018; 57: 1822-9.
33. SALLIOT C, DENIS A, DERNIS E *et al*.: Ultrasonography and detection of subclinical joints and tendons involvements in systemic lupus erythematosus (SLE) patients: A cross-sectional multicenter study. *Joint Bone Spine* 2018; 85: 741-5.
34. BURKARD T, TRENDELENBURG M, DAIKELER T *et al*.: The heart in systemic lupus erythematosus - A comprehensive approach by cardiovascular magnetic resonance tomography. *PloS One* 2018; 13: e0202105.
35. MAVROGENI S, KOUTSOGEORGOPOULOU L, MARKOUSIS-MAVROGENIS G *et al*.: Cardiovascular magnetic resonance detects silent heart disease missed by echocardiography in systemic lupus erythematosus. *Lupus* 2018; 27: 564-71.
36. MORONI G, VERCELLONI PG, QUAGLINI S *et al*.: Changing patterns in clinical-histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. *Ann Rheum Dis* 2018; 77: 1318-25.
37. BRODER A, MOWREY WB, KHAN HN *et al*.: Tubulointerstitial damage predicts end stage renal disease in lupus nephritis with preserved to moderately impaired renal function: A retrospective cohort study. *Semin Arthritis Rheum* 2018; 47: 545-51.
38. PAPADAKI E, FANOURIAKIS A, KAVROULAKIS E *et al*.: Neuropsychiatric lupus or not? Cerebral hypoperfusion by perfusion-weighted MRI in normal-appearing white matter in primary neuropsychiatric lupus erythematosus. *Ann Rheum Dis* 2018; 77: 441-8.
39. KUO CF, CHOU IJ, REES F *et al*.: Temporal relationships between systemic lupus erythematosus and comorbidities. *Rheumatology* (Oxford) 2018 Dec 19 [Epub ahead of print].
40. BARNADO A, CARROLL RJ, CASEY C, WHELESS L, DENNY JC, CROFFORD LJ: Phenome-wide association study identifies marked increased in burden of comorbidities in African Americans with systemic lupus erythematosus. *Arthritis Res Ther* 2018; 20: 69.
41. ESMAEILBEIGI F, POPE JE: Appropriate cardiovascular disease risk assessment in systemic lupus erythematosus may be lacking in rheumatology practice. *Clin Exp Rheumatol* 2018; 36: 526-32.
42. MOK CC, TSE SM, CHAN KL, HO LY: Effect of the metabolic syndrome on organ damage and mortality in patients with systemic lupus erythematosus: a longitudinal analysis. *Clin Exp Rheumatol* 2018; 36: 389-95.
43. MCGHIE TK, HARVEY P, SU J, ANDERSON N, TOMLINSON G, TOUMA Z: Electrocardiogram abnormalities related to anti-malarials in systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 545-51.
44. KNIGHT AM, TRUPIN L, KATZ P, YELIN E, LAWSON EF: Depression risk in young adults with juvenile- and adult-onset lupus: twelve years of followup. *Arthritis Care Res* 2018; 70: 475-80.

45. PARK DJ, KANG JH, LEE KE *et al*.: Association of depression with socioeconomic status, anticardiolipin antibodies, and organ damage in patients with systemic lupus erythematosus: results from the KORNET registry. *Clin Exp Rheumatol* 2018; 36: 627-35.
46. PERALTA-RAMIREZ MI, PEREZ-MARMOL JM, CASTANEDA-CABESTANY M *et al*.: Association between perceived level of stress, clinical characteristics and psychopathological symptoms in women with systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 434-41.
47. FIGUEIREDO-BRAGA M, CORNABY C, BERNARDES M *et al*.: Correlation between physical markers and psychiatric health in a Portuguese systemic lupus erythematosus cohort: The role of suffering in chronic autoimmune disease. *PloS One* 2018; 13: e0195579.
48. GLADMAN DD, DHILLON N, SU J, UROWITZ MB: Osteonecrosis in SLE: prevalence, patterns, outcomes and predictors. *Lupus* 2018; 27: 76-81.
49. KWON HH, BANG SY, WON S *et al*.: Synergistic effect of cumulative corticosteroid dose and immunosuppressants on avascular necrosis in patients with systemic lupus erythematosus. *Lupus* 2018; 27: 1644-51.
50. JORGE AM, LU N, ZHANG Y, RAI SK, CHOI HK: Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999-2014). *Rheumatology* (Oxford) 2018; 57: 337-44.
51. AZIZODDIN DR, JOLLY M, ARORA S, YELIN E, KATZ P: Patient reported outcomes predict mortality in lupus. *Arthritis Care Res* 2018 Aug 24 [Epub ahead of print].
52. ZEN M, IACCARINO L, GATTO M *et al*.: Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018; 77: 104-10.
53. TSELIOS K, GLADMAN DD, TOUMA Z, SU J, ANDERSON N, UROWITZ MB: Monophasic disease course in systemic lupus erythematosus. *J Rheumatol* 2018; 45: 1131-5.
54. RUIZ-ARRUZA I, LOZANO J, CABEZAS-RODRIGUEZ I *et al*.: Restrictive use of oral glucocorticoids in systemic lupus erythematosus and prevention of damage without worsening long-term disease control: an observational Study. *Arthritis Care Res* 2018; 70: 582-91.
55. KARASAWA K, UCHIDA K, KODAMA M, MORIYAMA T, NITTA K: Long-term effects of tacrolimus for maintenance therapy of lupus nephritis: a 5-year retrospective study at a single center. *Rheumatol Int* 2018; 38: 2271-7.
56. TANI C, ELEFANTE E, MARTIN-CASCON M *et al*.: Tacrolimus in non-Asian patients with SLE: a real-life experience from three European centres. *Lupus Sci Med* 2018; 5: e000274.
57. LI Y, FENG X: Efficacy and safety of tacrolimus in systemic lupus erythematosus patients with refractory thrombocytopenia: a retrospective study. *Lupus* 2018; 27: 60-5.
58. YANG TH, WU TH, CHANG YL *et al*.: Cyclosporine for the treatment of lupus nephritis in patients with systemic lupus erythematosus. *Clin Nephrol* 2018; 89: 277-85.
59. KASITANON N, BORIPATKOSOL P, LOUTHRENOO W: Response to combination of mycophenolate mofetil, cyclosporin A and corticosteroid treatment in lupus nephritis patients with persistent proteinuria. *Int J Rheum Dis* 2018; 21: 200-7.
60. FURIE RA, WALLACE DJ, ARANOW C *et al*.: Long-term safety and efficacy of belimumab in patients with systemic lupus erythematosus: a continuation of a Seventy-Six-Week Phase III Parent Study in the United States. *Arthritis Rheumatol* 2018; 70: 868-77.
61. ZHANG F, BAE SC, BASS D *et al*.: A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. *Ann Rheum Dis* 2018; 77: 355-63.
62. IACCARINO L, ANDREOLI L, BOCCI EB *et al*.: Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. *J Autoimmun* 2018; 86: 1-8.
63. MCCARTHY EM, SUTTON E, NESBIT S *et al*.: Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. *Rheumatology* (Oxford) 2018; 57: 470-9.
64. SERRIS A, AMOURA Z, CANOUI-POITRINE F *et al*.: Efficacy and safety of rituximab for systemic lupus erythematosus-associated immune cytopenias: A multicenter retrospective cohort study of 71 adults. *Am J Hematol* 2018; 93: 424-9.
65. GUALTIEROTTI R, BORGHI MO, GEROSA M *et al*.: Successful sequential therapy with rituximab and belimumab in patients with active systemic lupus erythematosus: a case series. *Clin Exp Rheumatol* 2018; 36: 643-7.
66. MASOUD S, MCADOO SP, BEDI R, CAIRNS TD, LIGHTSTONE L: Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab. *Rheumatology* (Oxford) 2018 Mar 19 [Epub ahead of print].
67. GOTTENBERG JE, DORNER T, BOOTSMA H *et al*.: Efficacy of Epratuzumab, an Anti-CD22 monoclonal IgG antibody, in systemic lupus erythematosus patients with associated Sjögren's syndrome: post hoc analyses from the EMBODY trials. *Arthritis Rheumatol* 2018; 70: 763-73.
68. CHENG LE, AMOURA Z, CHEAH B *et al*.: Brief Report: A randomized, double-blind, parallel-group, placebo-controlled, multiple-dose study to evaluate AMG 557 in patients with systemic lupus erythematosus and active lupus arthritis. *Arthritis Rheumatol* 2018; 70: 1071-6.
69. VAN VOLLENHOVEN RF, HAHN BH, TSOKOS GC *et al*.: Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet* 2018;392(10155):1330-9.
70. WALLACE DJ, FURIE RA, TANAKA Y *et al*.: Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2018; 392: 222-31.
71. LAI ZW, KELLY R, WINANS T *et al*.: Sirolimus in patients with clinically active systemic lupus erythematosus resistant to, or intolerant of, conventional medications: a single-arm, open-label, phase 1/2 trial. *Lancet* 2018; 391: 1186-96.
72. WILHELM M, WANG F, SCHALL N *et al*.: Lupus regulator peptide P140 represses B cell differentiation by reducing HLA class II molecule overexpression. *Arthritis Rheumatol* 2018; 70: 1077-88.
73. LIU J, HUANG X, HAO S *et al*.: Peli1 negatively regulates noncanonical NF-kappaB signaling to restrain systemic lupus erythematosus. *Nat Commun* 2018; 9: 1136.
74. BRIGHTBILL HD, SUTO E, BLAQUIERE N *et al*.: NF-kappaB inducing kinase is a therapeutic target for systemic lupus erythematosus. *Nat Commun* 2018; 9: 179.