Review

One year in review 2021: systemic lupus erythematosus

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Received on March 26, 2021; accepted in revised form on April 2, 2021.

Clin Exp Rheumatol 2021; 39: 231-241.

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

Competing interests: none declared.

ABSTRACT

In 2020 many contributions have been produced on SLE. Our critical digest of the recent literature will be focused on genetic factors that contribute to the development of the disease, novel potential therapeutic targets (including IL-23, IL-17, interferons and JAKs), diagnostic and prognostic biomarkers, classification criteria, clinical manifestations and comorbidities. We will then present new treatment options (with a special focus on belimumab, anifrolumab, tacrolimus, voclosporin and EULAR/ERA-EDTA recommendations for the management of LN) and treat-to-target strategy. Lastly, we will concentrate on some of the aspects that influence patients' disease perception and quality of life.

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune condition characterised by heterogeneous clinical manifestations and immunological abnormalities. The purpose of this review is to summarise the recent literature on pathogenesis, clinical manifestations and disease management in SLE. As in the previous annual reviews of this series (1-3), we performed a Medline search of English language articles on SLE published between January 1st and December 31st, 2020. We selected the most relevant papers, excluding case reports and reviews.

Pathogenesis and emerging therapeutic targets

The pathogenesis of SLE is still poorly understood and multiple factors are associated with the development of the disease, including genetic, epigenetic, immunoregulatory, ethnic, hormonal, and environmental factors.

As identified in several studies, the majority of SLE susceptibility genes are located in non-coding regions. A recent genome-wide analysis in 4.556 Chinese SLE patients and 9.451 healthy controls (4) showed an association between the A>G variation at rs13259960 in *SLEAR*, a long non-coding RNA, and susceptibility to SLE. In particular, this polymorphism leads to a down-regulation of SLEAR expression and enhances the apoptosis of peripheral blood mononuclear cells.

New data are emerging also on the immunological abnormalities that are implicated in the pathogenesis of SLE. Recently, Lee *et al*. (5) investigated the mechanisms of T helper (Th)17 differentiation and their association with SLE. Naïve $CD4^+$ T cells were cultured in Th17 polarising conditions and then treated with different cytokines; the results showed that Th17 differentiation was promoted by IL-23 through the phosphorylation of Signal Transducers and Activators of Transcription 3 (pSTAT3), which regulates epigenetic modifications. Interestingly, in patients with SLE (n=28), resting Th17 memory cells were characterised by a higher expression of IL-23R and pSTAT3; moreover, stimulation with IL-23 significantly increased pSTAT3 expression in patients with SLE but not in healthy controls.

Another recent study (6) investigated the role of IL-17 on plasma cells from patients with active SLE, inactive SLE and healthy controls. Researchers identified a subset of IL-17RA/RC^+ plasma cells that, upon IL-17 stimulation, reacted with a potent anti-dsDNA antibody production. This was positively correlated to increased circulating Th17 cell levels, serum autoantibody levels, and disease activity both in SLE patients and murine models. Furthermore, mice deficient for IL-17 or IL-17 receptor C exhibited a diminished plasma cell response and attenuated renal damage upon lupus induction.

Among other factors that could contribute to the pathogenesis of SLE, it is

worth mentioning Y-box binding protein 1 (YB-1), a cold-shock protein involved in the regulation of survival in activated T cells. Meltendorf *et al*. (7) analysed its expression in 25 SLE patients and 25 healthy controls, finding significantly lower levels in apoptosis-prone and activated T cells from SLE patients compared to non-apoptotic and activated T cells from healthy subjects. Interesting findings were also described in the study by De Groof *et al*. (8), in which researchers analysed Toll-like receptor 3 (TLR3) expression in HEK293 cells, myeloid-derived dendritic cells (moDCs) and SLE skin lesions. TLR3 overexpression in HEK293 cells amplified apoptotic responses, production of the Ro/SSA autoantigen and increased maturation of moDCs after exposure to UV irradiation; moreover, TLR3 resulted overexpressed in skin biopsies, suggesting an active role of this molecule in SLE inflammatory skin manifestations. The analysis of single nucleotide polymorphisms in TLR3 gene, however, excluded an association with an increased susceptibility to SLE both in a discovery cohort of 153 patients and 105 controls and in a confirmation cohort of 1.380 patients and 2.104 controls.

Take home messages on pathogenesis

- Genetic variations in long noncoding RNAs and low levels of YB-1 seem to predispose to SLE by influencing the apoptosis of mononuclear cells in the peripheral blood. (4, 7);
- Growing evidence suggests that IL-23 and IL-17 are involved in SLE pathogenesis, since they have a role in differentiation and in survival of T cells (5, 6).

Emerging potential therapeutic targets: phase I and II studies

Despite recent advances in understanding the molecular pathways that contribute to the development of the disease, the complex immune dysregulation and the heterogeneous clinical manifestations of SLE are still a challenge for targeted treatment.

Among B-cell-directed therapies currently used for SLE management we find belimumab (BEL) – a monoclonal antibody to BLyS specifically approved for seropositive and refractory SLE – and (with an off-label prescription) rituximab (RTX)- a monoclonal antibody to CD20 indicated for the treatment of haematological malignancies, ANCA-associated vasculitides, pemphigus, Rheumatoid Arthritis (RA). Recently, some researchers proposed a combined therapy with RTX and BEL to prevent B-cell repopulation and clinical relapses. In this regard, the results of a long-term follow-up of a phase II study (9) involving 15 SLE patients showed encouraging results, with 67% of patients achieving lupus low disease activity (LLDAS); furthermore, 75% of patients with lupus nephritis (LN) achieved a renal response and all patients with anti-dsDNA positivity converted to negative throughout the study.

Another B-cell directed therapy under investigation is atacicept, a human recombinant fusion protein directed both to BLyS and APRIL. Last year, Morand *et al*. (10) performed a *post hoc* analysis on the results of a phase II study (ADDRESS IIo), to evaluate the attainment of three treat-to-target endpoints (LDA, LLDAS, remission). The original study included 306 SLE patients who received weekly atacicept (75 or 150 mg) or placebo plus standard-of-care for 24 weeks. LDA (SLEDAI-2K≤2), LLDAS and clinical remission at week 24 resulted more stringent than SLE Responder Index (SRI)-4 and SRI-6 response, but were able to discriminate active treatment (150 mg) from placebo, suggesting that these endpoints may be meaningful outcome measures in future SLE clinical trials.

Since there is growing evidence that interferons (IFNs) play an important role in the pathogenesis of SLE, many IFN-directed agents are currently under evaluation for clinical use. Recently, a 36-week phase IIb, randomised, double-blind, placebo-controlled trial was performed to evaluate the efficacy and safety of the immunotherapeutic vaccine IFN-α kinoid (IFN-K) in 185 patients with active refractory SLE and positive IFN gene signature (11). Patients were randomised to receive intramuscular injections of IFN-K or placebo. At week 36, IFN-K induced neutralising anti-IFN-α2b serum antibodies in 91% of treated patients and a reduction of IFN gene signature in blood; moreover, there was a significant reduction of steroid-dose and an increased attainment of LLDAS in the IFN-K group, with an acceptable safety profile.

Novelties regarding anifrolumab, a monoclonal antibody to type I interferon receptor subunit 1, will be further described in detail below.

Among the biotechnological products recently proposed for SLE, it is worth mentioning ustekinumab, a monoclonal antibody already approved for the treatment of moderate to severe plaque psoriasis, psoriatic arthritis and Crohn's disease. Ustekinumab targets the p40 subunit of IL-12 and IL-23 cytokines, which are implicated in SLE pathogenesis. A phase II multicenter prospective randomised double-blind placebo-controlled crossover study (12) evaluated the role of ustekinumab in 102 patients with active SLE despite conventional therapy. Patients were randomly assigned (3:2) to receive either ustekinumab (intravenous loading dose of 260, 390 or 520 mg depending on body weight followed by 90 mg subcutaneous injections every 8 weeks) or placebo in addition to standard therapy. After 24 weeks, placebo group was switched to subcutaneous 90 mg ustekinumab every 8 weeks, while the original ustekinumab group continued to receive the same therapy until week 40. A sustained response was observed in those patients who received ustekinumab from baseline through week 40. Interestingly, increased response rates were also noted in patients from the placebo group who crossed over to ustekinumab.

Also kinase inhibitors are under investigation for the treatment of SLE. Dörner *et al*. (13) analysed the results of a phase II, 24-week, randomised, placebo controlled double-blind study trial with baricitib (BAR), a JAK1 and JAK2 inhibitor. Blood samples from 274 patients were processed to characterise gene expression and serum cytokines. The results confirmed that, also in SLE, JAK/STAT pathways have a crucial role in the pharmacological effect of BAR: changes in the expression of STAT1/STAT2 target genes were linked

with response to treatment and serum IL-12p40 and IL-6 decrease.

A randomised, double-blind clinical trial was recently conducted to assess safety and efficacy of two selective kinase inhibitors in patients with lupus membranous nephropathy, a subtype of LN that generally does not respond well to conventional immunosuppressive treatment. Five patients were treated with filgotinib, a JAK1 inhibitor approved for RA, while 4 patients were treated with lanraplenib, a spleen tyrosine kinase (SYK) inhibitor. After 16 weeks, a reduction of 24-hour urine protein excretion was recorded in the filgotinib group, while no improvement was seen in patients treated with lanraplenib (14).

Lastly, clopidogrel was proposed as add-on strategy in SLE, following the observation that soluble CD40L ligand (sCD40L) concentrations in blood are correlated with disease activity in SLE. sCD40L is a cleaved form of CD40L, shed by activated T lymphocytes and platelets. In this study, 18 stable SLE patients were enrolled in a single-arm, open-label, monocentric phase I/II trial and received clopidogrel for 12 weeks in addition to standard SLE therapies (15). Clopidogrel was well tolerated, but the primary endpoint (a significant change in sCD40L plasmatic concentration after 12 weeks) was not statistically met, although a temporal relationship between clopidogrel exposure and sCD40L levels was recorded, suggesting that this drug could decrease platelet activation by interfering with platelet CD40L and CD62 expression.

Take home messages on emerging therapeutic targets

- Phase II trials of JAK inhibitors, ustekinumab and IFN-directed agents have shown preliminary positive results (11-13);
- A combined therapy with RTX and BEL could be useful in refractory cases (9).

Biomarkers

During the last decades, there has been an increasing interest in biomarkers not only for lupus diagnosis but also for monitoring and predicting upcoming flares and response to therapies. Although many biomarkers have been discovered, only few are validated and used in the clinical practice. The latest studies on this topic are enlisted in this section.

A cross-sectional Japanese (16) study demonstrated that serum levels of Galectine-9 (Gal-9) were significantly increased in patients with SLE compared with the control group. Moreover, Gal-9 levels were correlated with disease activity and with SLE-related organ involvement. Li *et al*. (17) showed that two serum exosomal microRNA, miR-21 and miR-155 were higher in SLE patients, compared to healthy controls; miR-21 and miR-155 were positively correlated with proteinuria. Similarly, hsa_circ_0000479 (a circular RNA) in peripheral blood mononuclear cells was increased in SLE patients, proving a possible diagnostic role.

Two studies analysed the possible role of long non-coding RNA (lncRNAs) as biomarkers for SLE diagnosis. The first (18) found that the expression of lnc-FOSB-1:1 was significantly decreased in neutrophils of SLE patients compared to other connective tissue diseases or healthy controls; more importantly, decreased lnc-FOSB-1:1 expression was associated with lupus nephritis. The second study (19) identified TCONS_00483150 as diagnostic biomarker as it could be able to distinguish patients with SLE (active or stable disease) from healthy controls and those with rheumatoid arthritis.

Another recent study (20) demonstrated that both anti-α-enolase Ab and RDW were significantly higher in SLE patients than in the healthy control and their presence correlated with disease activity.

Also glycoprotein acetylation (GlycA) could be a good marker of disease activity, as highlighted in the study by Dierckx *et al*. (21): GlycA levels, which were found to be increased in several inflammatory disorders, had a positive correlation with SLE disease activity and their value was higher in proliferative nephritis than in non-proliferative nephritis.

Another study (22) investigated the role of circular RNAs as biomarkers of LN: hsa_circ_0082688, hsa_circ_0082689 and hsa_circ_0008675 serum levels were significantly higher in patients with LN respect to SLE patients without renal involvement, patients with non-SLE nephritis and healthy controls.

Other interesting new data emerged on proinflammatory cytokines/chemokines such as TNF-like weak inducer of apoptosis (TWEAK) and neutrophil gelatinase-associated lipocalin (NGAL); their serum (s) and urine (u) levels correlated with disease activity in SLE. Moreover, higher levels of (s)TWEAK were found in patients with active renal SLE (23).

An interesting study (24) showed that the absolute number and proportion of Milk fat globule epidermal growth factor 8 (MFG-E8) positive monocytes to total monocytes were significantly higher in patients with active SLE; the proportion was also significantly correlated with known disease activity parameters such as SLEDAI-2K score, serum levels of anti-ds-DNA antibodies, complement and C1q.

Another study (25) analysed genetic variants of Tissue factor (TF) and Human apolipoprotein H (APOH) and demonstrated that TF rs3917615 and rs958587 and APOH rs4581 might predispose to joint involvement in SLE.

Finally, as shown by Schaier *et al*. (26), an imbalance between $CD4^+$-regulatory T-cells (Tregs) and $CD4^+$-responder T-cells (Tresps) seems to correlate with occurrence of disease flares in SLE patients.

Regarding potential biomarkers of renal involvement, a Mexican study (27) demonstrated that urinary CD163 levels were higher in patients with active LN than in patients with active extrarenal SLE, inactive SLE, and other glomerular diseases, and correlated with disease clinical severity, histologic class, and the histologic activity index.

Another study (28) measured urinary levels of transferrin and ceruloplasmin in 120 patients with SLE. Urinary levels of these two biomarkers were significantly higher in patients with LN compared to those without LN. Similarly, urinary levels of both biomarkers were significantly higher in patients with active LN compared to those with inactive LN.

An American study (29) screened the presence of 1000 proteins from urine samples of SLE patients, using a novel, quantitative planar protein microarray. 64 urinary proteins were significantly elevated in the samples obtained by SLE patients. Among these proteins Angptl4, L-selectin and TGFβ1 seemed to be potential biomarkers for tracking disease activity in LN. Davies *et al*. (30) also analysed a urinary protein panel to identify potential LN biomarkers. The results showed that levels of transferrin, AGP-1, ceruloplasmin, MCP-1 and sVCAM-1 were higher in SLE patients with active LN when compared with patients without active LN; furthermore, a combined model of five urine proteins, namely LPGDS, transferrin, AGP-1, ceruloplasmin, MCP-1 and sVCAM-1 predicted response to rituximab treatment at 12 months (AUC 0.818).

Also immunoglobulin binding protein 1(IGBP1) plasma levels could be useful LN biomarkers. In particular, Kwon *et al*. (31) observed that IGBP1 plasma levels were higher in patients who developed LN, compared with patients who did not develop LN; interestingly, the combination of plasma IGBP1 and anti-dsDNA antibodies was a highly specific (97%) composite predictor for the development of LN.

Some biomarkers are not only predictive of LN development but can also predict long-term renal impairment. A recent study (32), for example, demonstrated that urinary (U) levels of sVACAM-1 and sALCAM are able to distinguish SLE patients with active renal involvement from patients with quiescent or no prior nephritis; furthermore, high U-sVCAM-1 levels may indicate patients at increased risk for long-term renal function loss.

Another study (33) observed that patients with chronic kidney disease (CKD) had higher serum levels of Slit2 than patients with no CKD and, in patients with CKD, Slit2 levels were positively correlated with serum creatinine, urine protein, and glomerular filtration rate.

A Korean group (34) investigated the effect of hyperuricaemia on the progression of kidney function in patients with LN using data of KORNET, a prospective longitudinal SLE registry in the Republic of Korea. The results showed that complete remission at 1 year was less frequent in the higher uric acid (UA) group, whereas CKD and end-stage renal disease were more prevalent; levels of UA >7 mg/dL seemed to be a significant predictor of progression to CKD in patients with LN.

Since SLE patients are prone to accelerated atherosclerosis and increased incidence of cardiovascular (CV) disease, several studies tried to identify potential biomarkers that correlate with this risk. A possible useful biomarker is serum sCD163, whose levels are positively correlated with the progression of carotid plaque in SLE patients (35).

Considering that leptin and TWEAK have been correlated to subclinical atherosclerosis and that galectin-3-binding protein (G3BP) is linked to a pro-thrombotic environment through type I interferon activation, Peretz *et al*. (36) measured serum levels of G3BP, interferon gamma-induced protein 10 (IP-10), sCD163, TWEAK and leptin in 162 patients affected by SLE. The results of a univariable regression analysis showed that only G3BP levels were significantly associated with an increased risk of venous thromboembolism in SLE patients.

Take home messages on biomarkers

- Gal-9, miR-21, miR-155, lnc-FOSB-1:1, TCONS_00483150, hsa_circ_0000479, anti-α-enolase Ab and RDW were able to distinguish SLE patients from controls (16-20);
- GlycA levels, TWEAK, NGAL, MFG-E8 could be useful biomarkers to monitor disease activity (21, 23, 24);
- hsa_circ_0082688, hsa_circ_0082689 and hsa_circ_0008675, IGBP-1, urinary CD163, transferrin, AGP-1, ceruloplasmin, MCP-1 Angptl4, L-selectin, TGFβ1 and sVCAM-1 levels were able to distinguish patients with active LN from patients without renal involvement (22, 27-32).

Classification criteria

Recently, the European League Against Rheumatism (EULAR) jointly with the ACR have proposed new classification criteria, introducing the ANA positivity as an obligatory entry criterion, and the additive, weighted multicriteria system (37). Over the past year, several studies evaluated the accuracy of the new criteria among wider and diversified populations. An international multicentre study evaluated the performance of the new EULAR/ACR and the Systemic Lupus International Collaborating Clinics (SLICC) 2012 and ACR 1982/1997 criteria with regard to disease duration, sex and race/ethnicity (38). The EULAR/ACR 2019 criteria performed well in both genders and across different ethnic groups (White, Black, Hispanic, and Asian patients). Additionally, the new criteria performed well also among patients with early disease (less than 3 years from disease onset) (39), with a 97% sensitivity and a 96% specificity. The sensitivity of the EULAR/ACR and previous classification criteria was assessed against physician diagnosis in a cohort of patients diagnosed with SLE (n=690) or control diseases (n=401) both at the time of diagnosis and at the last patient visit assessment. Both the EULAR/ACR and SLICC criteria had higher sensitivity (88.6% and 91.3%, respectively) than the ACR criteria (85.7%), with the EULAR/ACR having higher specificity than the other two sets (97.3% *vs*. 93.0–93.8%). By analysing patients with disease duration <3 years, a significantly increased sensitivity of the EULAR/ACR (87.3%) and SLICC (91.4%) as compared with the ACR criteria was observed. In this study, only 76.7% of patients with SLE met all three criteria suggesting non-overlapping groups. Notably, unclassified patients had a high prevalence of moderate/severe manifestations and SLICC/ACR organ damage (30–50%).

Regarding childhood-onset lupus (cSLE), Ma *et al*. (40) compared through a retrospective chart review study the performance of the three sets of classification. With the 2019 EULAR/ACR criteria, the most common items were autoantibodies, complement reduction and, among clinical criteria, articular and haematologic involvement. With the 2012 SLICC criteria, the most common immunologic criteria were positive anti-dsDNA, low complement, and positive anti-Sm, whereas

the most common clinical criterion was synovitis. These data suggest that immunologic abnormalities, cytopenias and arthritis are common as initial presentation in paediatric lupus patients. For these patients, both the 2019 EULAR/ACR criteria and the 2012 SLICC criteria were more sensitive than the 1997 ACR criteria, with similar specificity.

Lastly, Carneiro *et al*. (41) performed a direct comparison of the three classification criteria sets in a cohort of adult patients to investigate their predictive role regarding organ damage and mortality over a 10-year follow-up period. The analysis showed that in patients with higher EULAR/ACR scores at the time of diagnosis, there was an increased incidence of organ damage that persisted after adjustment for age and sex. No associations were found between the ACR and SLICC sets and outcomes.

Clinical manifestations

In 2020, EULAR published the update of the joint EULAR and European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) recommendations (42) for the management of LN. Among the most striking new aspects introduced, the recommendations defined the treat-to-target as the achievement of a proteinuria <0.5–0.7 g/24 hours by 12 months (complete clinical response). In this view, Moroni *et al*. (43) tested the EULAR/ERA-EDTA definition of response in a large cohort of patients with a long follow-up. After a 12-month therapy, 58% of patients achieved a complete response, according to the aforementioned definition.

During a median follow-up of 10 years, however, 53/381 patients developed CKD.

In multivariable analysis, a lack of EULAR/ERA-EDTA response at 12 months, low C4 levels and persistent arterial hypertension were independent predictors of renal failure. Notably, both complete and partial responses at 1 year correlated with good renal survival (survival rate of 95.2%, 87.6% and 55.4% in patients with complete, partial and no response at 12 months, respectively).

In the neuropsychiatric field, Hanly *et al*. (44) expanded the knowledge on peripheral nervous system (PNS) manifestations by analysing a large, multiethnic/multiracial, prospective, inception cohort of SLE patients. The overall frequency of PNS events in the study was 7.6%, with a rising trend over the last decade. Peripheral neuropathy (41.0% of PNS events), mononeuropathy (27.3% of PNS events), and cranial neuropathy (24.2% of PNS events) were the most frequent events. Longer time to resolution was associated with a previous history of neuropathy, peripheral nerve involvement, older age at SLE diagnosis, and higher SLEDAI-2K scores. The outcome, however, was favourable for most patients and resolution occurred in 51% of patients by the end of the study.

Comorbidities

Comorbidities contribute substantially to the disease burden in patients with SLE; over the past year special attention was paid to cardiovascular (CV) and atherosclerotic vascular (AV) domains. For example, Urowitz *et al*. (45) evaluated the prevalence and the accrual of AV events (AVEs) in a multiethnic, prospective inception cohort that included 1848 patients with a recent diagnosis of SLE. One hundred seventy AVEs were identified in 113 patients after their enrolment visit, with an incidence of 4.56 per 1,000 patient-years. In multivariate analyses, lower AVE rates were associated with antimalarial treatment, while higher AVE rates were associated with any prior vascular event and a body mass index of >40 kg/m^2. A prior AVE increased the risk of subsequent AVEs. Interestingly, the prevalence of AVE in this study is much lower than in previously published data. This may be related to a better control of both disease activity and classical risk factors, as suggested by the authors.

In inflammatory diseases, indeed, assessing both traditional CV and disease-specific factors has become mandatory. In this view, a study evaluated the prevalence of traditional CV risk factors in a cohort of patients with SLE and estimated the 10-year risk of CV events with three different algorithms, namely the Framingham score, the American College of Cardiology/American Heart Association (ACC/AHA) score and the QRISK3 (46). The study demonstrated that the QRISK3 – a validated algorithm that in addition to traditional risk factors considers specific items such as the presence of SLE and the regular intake of steroids – was able to classify a greater number of patients at high risk of developing CV disease in the following 10 years in comparison with the other two classical algorithms. The superiority of QRISK3 algorithm was observed especially in the younger age group (patients with less than 40 years), in presence of CKD and in patients with chronic intake of glucocorticoids.

Regarding specific risk factors, Tzelios *et al*. (47) evaluated the impact of hypertension - defined with the new ACC/AHA criteria (blood pressure ≥130/80 mm Hg)- in a cohort of 1532 SLE patients from the Toronto Lupus Clinic.

Patients- with at least 2 years of follow-up and no prior CV- were divided into three groups according to their mean blood pressure over that period (≥140/90 mm Hg, 130–139/80–89 mm Hg and <130/80 mm Hg). A mean blood pressure of 130–139/80–89 mm Hg over the first 2 years was independently associated with the occurrence of CV events, confirmed after adjustment for all traditional and disease-related atherosclerotic risk factors.

Take home messages on clinical manifestations and comorbidities

- EULAR/ERA-EDTA response at 12 months, low C4 levels and persistent arterial hypertension are associated with a poor renal outcome (43);
- Regarding SLE neuropathy, patients with a previous history of neuropathy- especially the peripheral subtype-, older age at SLE diagnosis, and higher SLEDAI-2K scores had longer duration of symptoms (44);
- QRISK3 algorithm was superior to Framingham score and ACC/AHA score in predicting CV events in SLE patients (46).

Therapies and treatment strategies

Until 2020 the only drug specifically approved for SLE was belimumab, a human monoclonal antibody to BLyS,

available for adult patients with active, seropositive SLE.

The recently published long-term open-label extension study of the phase III trials (BLISS-52 and BLISS-76) (48) confirmed good efficacy and safety profile of the drug, with a retention rate after 8 years of 49.9% (368/738 patients). Similarly to the phase II continuation study, the incidence of adverse events (AEs), severe AEs (SAEs) and AEs leading to discontinuation was higher in the first year, with a subsequent stabilisation or decline through the remainder of the study. Headache was the most frequently reported AE, followed by upper tract infections, diarrhoea and arthralgias; in both phase II and phase III extension studies, cellulitis and pneumonia were among the most frequently reported SAEs. 1.1% of patients experienced malignancies, peaking at study year 3-4. 12.9% of patients developed an opportunistic infection, peaking in study year 0-1. Depression was reported in 11.7% of patients (95% with mild symptoms), with incidence decreasing over the course of the study. Throughout the study, there were 1 suicidal ideation and 2 suicidal attempts (not completed), providing evidence to alleviate concerns regarding suicidality while receiving belimumab. Death occurred in 11 patients during the study, but only in one case (cardiac failure) the AE was considered as possibly related to belimumab. Laboratory parameters and mean SLICC/ACR Damage Index score generally remained stable over time, indicating low drug toxicity and no organ damage accrual.

Recently, the European Commission and the FDA extended the indication of belimumab also to children 5 years and older. This approval was based on the results of PLUTO (Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy) (49), an ongoing phase II multicentre, double-blind, placebo-controlled trial in which 93 patients (13 children and 80 adolescents) were randomised to receive either intravenous belimumab (10 mg/kg) or placebo every 4 weeks, plus standard SLE therapy. Within the limits of the short period of observation (52 weeks) and the small sample size, the benefit-risk profile of belimumab was consistent with previous studies on adult patients, allowing an extension of the indication also to childhood-onset SLE.

Another promising biological drug is anifrolumab, a monoclonal antibody to type I interferon receptor subunit 1. After a partial failure of TULIP-1 (50), AstraZeneca published the results of a second phase III trial (TULIP-2) (51), considering as primary endpoint the response rate at week 52, defined using the BILAG-based Composite Lupus Assessment. A total of 362 patients received the randomised intervention (IV monthly infusion of anifrolumab 300 mg or placebo) for 48 weeks. The primary endpoint was met in 47.8% of patients in the anifrolumab group (*vs.* 31.5% in the placebo group), with a positive impact on the severity of skin manifestations and a significant decrease in the glucocorticoid dose. Conversely, there were no significant differences in the annualised rate of SLE flares and in the number of tender and swollen joints. Notably, the drug was well tolerated, with a retention rate of 85% at 48 weeks (*vs.* 71.4% in the placebo group). Adverse events that occurred at a frequency at least twice that of the placebo group were bronchitis, upper respiratory infection and herpes zoster; one patient died from pneumonia.

Long-term safety and tolerability of IV anifrolumab were recently confirmed by the three-year open-label extension of MUSE, a phase IIb randomised controlled trial. This study (52) confirmed an acceptable safety profile of anifrolumab, with sustained improvement in disease activity, quality of life and serology in patients with moderately-to-severely active SLE, with a retention rate of 63.8% at three years.

New therapeutic options in lupus nephritis treatment

For many years, mycophenolate (MMF) and cyclophosphamide (CY) in monotherapy have been considered cornerstones for the induction therapy of LN, but there is increasing evidence that calcineurin inhibitors (CNI) and multitargeted therapy are valid alternative options.

The most recent ERA-EDTA recommendations (42) confirmed for class III and IV LN a first-line induction treatment with MMF 2–3 g/day or low-dose IV CY (500 mg x 6 biweekly doses) in combination with glucocorticoids (GCs); CNI/MMF combination and high-dose CY are alternative options for nephrotic-range proteinuria and adverse prognostic factors, while RTX should be reserved for refractory cases. Particular attention was paid to GC use: the experts recommended administration of IV methylprednisolone pulses followed by lower doses of daily GCs (oral prednisone 0.3–0.5 mg/kg/day) to decrease the cumulative dose.

MMF, in combination with GCs, was also the first-line choice for pure membranous LN.

Notably, the recommendations remarked the importance of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as adjunct treatment for LN, as well as anticoagulation in patients with antiphospholipid syndrome.

Among CNI, tacrolimus (TAC) is a relatively old drug widely used in nephrology for the prevention of transplant rejection. A recently published long-term randomised controlled study (53) compared the 10-year outcome of LN in 150 Chinese patients treated with MMF or TAC followed by azathioprine maintenance. Renal response rate and renal flare rate were similar between MMF and TAC-treated patients, with no significant differences in the cumulative incidence of end-stage renal disease and death.

During the drafting of this year's review, a novel calcineurin inhibitor – voclosporin (Lupkynis®, Aurinia Pharmaceuticals) – was approved by the US Food and Drug Administration (FDA), making it the first oral treatment licensed for active lupus nephritis (LN) in the US (54). This approval was based on the results of a 52-week Phase III multicentre, randomised, double-blind, placebo-controlled study (AURORA), which included 357 patients with biopsy-proven active class III, IV and V LN (55).

Patients were randomised to voclosporin (VCS) or placebo in combina-

tion with MMF (1 g BID) and rapidly tapered oral steroids. The combination therapy with MMF and low-dose VCS (23.7 mg twice daily) was more effective than placebo in inducing renal remission (40.8% for the VCS arm and 22.5% for the control arm (OR: 2.65; 95% CI: 1.64, 4.27; $p<0.001$), without significant differences between Hispanic/Latino and non-Hispanic/Latino patients. Differently from the phase II study (AURA-LV) (56), the overall incidence of severe adverse events was similar in both groups (VCS 20.8% and control 21.3%); moreover, blood pressure, glucose and lipid levels were not significantly increased at week 52, compared to placebo. As we write this paper, only partial data are available; further studies will be needed to assess the long-term safety of VCS and to compare the efficacy of VCS + MMF 1 g BID with the standard induction therapy for moderate-severe LN, *i.e.* MMF 1.5 g BID or intravenous CY 500 mg every 2 weeks for 6 infusions.

Another relevant contribution regards a phase III multinational randomised, double-blind trial (57) in which 448 patients with biopsy-proven, active and seropositive LN were randomised 1:1 to belimumab or placebo plus standard therapy within 60 days from standard induction therapy. Exclusion criteria were dialysis within 1 year, eGFR less than 30 ml per minute, previous failure of both CY and MMF induction, cyclophosphamide induction therapy within 3 months before the trial and B-cell–targeted therapy (including belimumab) within 1 year before randomisation. Renal response and complete renal response at 104 weeks were significantly ($p<0.05$) higher in belimumab group (43% and 30%, respectively) *versus* 32% and 20% in placebo group. Safety of belimumab plus standard therapy was similar to that of standard therapy alone, suggesting a possible benefit from the combined therapy.

Take home messages on treatment

- Belimumab has been recently approved for paediatric use (49) and can be considered as an add-on therapy for adult patients with active LN (57);
- Anifrolumab is a monoclonal antibody to type I interferon receptor subunit 1. Data at 54 weeks show good tolerability, amelioration of skin manifestations and steroid-sparing effect (51);
- TAC and MMF in monotherapy had similar efficacy at 10 year; VCS+MMF 1 g BID was superior to MMF 1 g BID. VCS has recently received marketing authorisation in the US (53-55).

Treat-to-target and patient-reported outcomes

Since when the principle of "treat to target" (T2T) has been applied in SLE and the recommendations of an international and multidisciplinary task force have been published (58), the real challenge has been the definition of the most meaningful treatment targets.

Certainly, remission of the disease and LLDAS are among the most desirable goals.

In the past year, some authors focused their attention on the predictors of the achievement of remission/LLDAS and the impact of these targets on the natural history of the disease.

Saccon *et al*. (59) explored, in a large multicentre SLE cohort, the performance of the three major items included in the DORIS definition of remission (60) (cSLEDAI=0, PGA <0.5 and prednisone ≤5 mg/day) in capturing a remission status and in predicting damage accrual. They observed that cSLEDAI=0 was the easiest definition of remission that could be attained in real life, being able to predict damage accrual with a consistent degree of accuracy. The exclusion of a cut-off for prednisone (PDN) could imply that high dose glucocorticoids may mask disease activity. Nevertheless, the authors found that adding PDN ≤5mg/day to cSLEDAI=0 did not increase the performance against damage of cSLEDAI=0 in the short/medium term (5 years). These observations seem to support cSLEDAI=0 to be considered the first target to achieve in a short- to mid-term follow-up, while cSLEDAI=0 plus PDN ≤5mg/day could be considered the best target in the medium/long term, since it is well known that even low dose of glucocorticoids lead to damage accrual in the longer run. If clinical remission seems to be an achievable target, remission off treatment seems to be a more difficult and controversial goal to achieve and maintain.

Jakez-Ocampo *et al*. (61) retrospectively described the clinical characteristics of a group of SLE patients with a very prolonged state of clinical remission off treatment. In a cohort of 2121 SLE patients from a referral center in Mexico, they identified 44 patients with at least 10 years of remission without any treatment (including antimalarials) and 88 patients with chronically active course. Apart from a trend to be younger at diagnosis in the chronically active group, overall the initial clinical pattern of disease was quite similar in patients that in the future would have achieved complete remission, including patients with very active disease at baseline. These results seem to suggest that independently of the initial manifestations, remission is a possible target for patients with SLE. As expected, patients in prolonged remission had less accrual damage when compared with chronically active group.

For the first time, Gao *et al*. (62) compared the time to achieve each state of LLDAS (63) and DORIS definition of remission (60), with a long-term follow-up period, in a Chinese SLE cohort. Only treatment-naïve patients were included to avoid the confounding effect of the previous treatment. 18.8% of patients achieved LLDAS in the first year of follow-up, supporting that LLDAS is an attainable target at the early treatment stage. The median time to clinical remission on treatment (RONT) was 2.6 years, which was nearly 2-fold the time to LLDAS. Interestingly, when the definition of prednisone dose in LLDAS was substituted by ≤5 mg/day (LLDAS5), the frequencies of patients and the time to achieve LLDAS5 were more similar to those of clinical RONT, rather than LLDAS. When considering the different components of LLDAS and DORIS, only the achievement frequency of prednisone dose during follow-up was significantly decreased (≤7.5 mg/day in 92.2% patients, ≤5 mg/day in 78.4% patients). These findings suggested that prednisone dose,

rather than disease activity (PGA or SLEDAI), was the key obstacle for patients who achieved LLDAS to further achieve remission.

Babaoğlu *et al*. (64) evaluated time to LLDAS in the Hopkins Lupus Cohort. Compared to the Chinese cohort, Babaoğlu reported a shorter median time to LLDAS (1.1 *vs*. 1.4 years), maybe due to the lower baseline disease activity. Though different time needed for LLDAS achievement, the cumulative probability of LLDAS achievement in the first 5 years was similar between the Chinese cohort and the Caucasian patients from Hopkins Lupus Cohort (93% of patients), indicating that the majority of patients can achieve LLDAS. However, in the Hopkins Lupus Cohort the time to LLDAS was found to be longer in African-American SLE patients, even after adjustment for renal activity, and the probability of LLDAS achievement in the first 5 years was lower in African-American (82%) compared to Caucasian patients. These findings point to the need to include African-American SLE patients in both clinical and pharmaceutical research, as it is not possible to generalise from studies from Europe and Asia.

Recent data from the Tromsø Lupus Cohort, which includes patients with SLE in the two northernmost counties in Norway, showed that 33.5% of patients spent at least half of their follow-up time in LLDAS (LLDAS-50). In this longitudinal population-based study (65), the authors demonstrated that achievement of LLDAS-50 was associated with a significant reduction in severe damage and also with a reduction in mortality.

Among the unmet needs of T2T strategy in SLE, studying non-inflammatory factors influencing patients' Health Related Quality of Life (HRQoL) and developing interventions to improve such factors represent some of the most important issues to be addressed.

A lack of concordance between physicians' evaluation of disease activity and damage and patients' HRQoL is commonly found in SLE. Some physicians even fear looking at the patient's perspective, because of uncertainties of how to face and treat it. (66).

A recent meta-analysis (67) explored the relationship between disease activity, organ damage and HRQoL – assessed by both generic and disease-specific scales – in SLE. In all eight domains of SF-36, disease activity showed modest correlation with HRQoL, with bodily pain being highest and physical functioning being the lowest. Lupus-specific QoL measurements, like the LupusPRO questionnaire, was relatively sensitive to the changes of disease activity and organ damage compared with generic SF-36 scale.

According to this work, mental health-related domains showed less relationship with clinical outcomes, such as organ damage and remission status, when compared to SF-36 domains related to physical well-being.

The authors also wanted to further examine the effect of geographical differences of SLE patients on the correlation between disease activity and HRQoL. A subgroup analysis was then conducted in patients enrolled from various regions including Africa, Europe, Asia, and America. Correlation coefficients between disease activity and bodily pain, general health, vitality, and social functioning were statistically significant in African and European SLE patients. Organ damage had stronger negative correlations with SF-36 domains in Asian SLE patients compared with American and European patients. However, SDI was significantly correlated with physical functioning in SLE patients from all regions. These results seem to suggest that it is less likely to optimising the mental health-related quality of life by only controlling disease activity and damage accrual.

It is well known in the literature that mood disorders are very frequent among SLE patients. This is also confirmed in a recent study by Cui *et al*. (68): in their cohort, they found a high prevalence of depression and anxiety symptoms (79.5% and 86.8%, respectively). Interestingly, they found that illness uncertainty was positively associated with psychological distress and may contribute to the development of depression and anxiety symptoms in women with SLE.

Among subjective factors influencing patient perception of disease status, fatigue represents one of the most prominent symptoms of SLE and a major contributor to QoL, although is only addressed in a few instruments used in clinical practice to monitor the disease. In recent years, a great amount of literature has been focusing on fatigue in lupus.

Obviously, it is important to distinguish between fatigue in patients with high disease activity, in whom remission or at least low disease activity should be targeted, and fatigue in inactive patients, with a very high load of anxiety and depression, for whom psychological and behavioural assessment represents a key step (69).

In a large Italian cohort of SLE patients, fatigue revealed to have a strong negative impact on HRQoL and patient perception of the disease burden. Importantly, in this study (70), fatigue was irrespective of disease activity but significantly influenced by the presence of fibromyalgia.

Clinical manifestations with an impact on daily activities, although not severe, represent the most important patient concern, while they are often overlooked by the treating physician.

According to a recent study (71), past and ongoing joint involvement, a concomitant diagnosis of fibromyalgia and ongoing glucocorticoid treatment may represent the most important variables determining the poor concordance between patient and physician perspective on the disease.

Actually, chronic pain represents a pervasive symptom in SLE patients.

A cross-sectional analysis (72) of patient-reported data from a population-based registry including 766 individuals with SLE, examined predictors of pain intensity and interference, defined as pain that hinders major life activities. Patients reporting increased disease activity also reported higher pain intensity and interference. However, disease activity and organ damage explained only 32–33% of the variance in pain intensity and interference. Sociodemographic factors accounted for an additional 4–9% of variance in pain outcomes, with older age and black race being associated with increased

pain intensity and higher socioeconomic status being protective for pain outcomes. Finally, psychosocial/behavioural factors accounted for the final 4% of variance. These findings suggest that multilevel interventions may be needed to tackle the negative impact of pain in SLE.

Clinical symptoms, biological information and patient-reported outcomes (PROs) are therefore all relevant targets and should be integrated in the management of SLE, promoting an active involvement of patients in their care process and in the management of the disease.

When faced with SLE, which is a chronic disease, patients must implement coping strategies. Farhat *et al*. (73) analysed 158 SLE patients and identified four clusters depending on the predominant strategy of coping (emotion-centered coping, problem-centered coping and search for social support). They discovered relationships between coping, psychological distress and perceived benefits of treatment. In particular, the cluster of patients with low problem-centered coping, high emotion-centered coping and the lowest search for social support had worse quality of life and more psychological distress; felt more anxious and depressed.

Patient education has become an integral part of patient empowerment. In this context, patients' knowledge of the disease is not the only parameter to consider for a personalised educational therapy, but psychological parameters, such as coping, must also be considered to ensure the best possible quality of life. For educational therapy purposes, it seems important not to group patients with the same coping style, as heterogeneous groups will enable patients to share their experiences and learn from the coping strategies of others.

Take home messages

- Clinical remission is attainable in real life, for patients who are unable to reach clinical remission, LLDAS is an alternative target of treatment, being able to reduce severe damage accrual (59-65);
- The LupusPRO survey tool was more sensitive than generic SF-36 scare in recognising changes of disease activity and organ damage (67);
- Anxiety, depression, chronic pain and fatigue have a negative impact on patients' quality of life and should therefore be assessed and properly treated; patients should be educated and encouraged to self-empowerment (67-73).

Conclusions

Despite the pandemic outbreak of COVID-19 disease, in 2020 many contributions have been published on SLE, providing new insights into biochemical and clinical aspects of this complex disease. A cure for SLE is still a long way off but, hopefully, through precision medicine we will be able to improve patients' disease course and quality of life.

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