Review

One year in review 2022: systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic multisystem auto-immune disease with extremely varied clinical manifestations and a complex pathogenesis. New insights in SLE about pathogenetic pathways, biomarkers, and data on clinical manifestations are progressively emerging, and new drugs and new therapeutic strategies have been proposed to improve the control of disease activity. Thus, this review is aimed to summarise the most relevant data about SLE emerged during 2021, following the previous annual review of this series.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease with a wide range of clinical manifestations that predominantly affects women. We performed a Medline search of English language articles published from 1st January to 1st December 2021 using MESH terms and free text words for the following search keys: systemic lupus erythematosus AND pathogenesis, biomarkers, clinical manifestations, comorbidities, remission, low disease activity, patients reported outcomes, therapy. We reviewed all the papers and selected the most relevant articles regarding adult SLE excluding reviews and case reports.

Thus, the aim of this review was to describe the most relevant data on SLE that emerged during the past year following the previous "One year in review" of this series (1-3).

Pathogenesis

SLE pathogenesis is the result of complex interactions between genetic, epigenetic, immunoregulatory, ethnic, hormonal and environmental factors, and several key points of these multifactorial connections are still unclear. It is well known that SLE, as other autoimmune conditions, is a female-predominant disease. The origins of this sex bias are poorly understood, suggesting the presence of hormonal or X-linked genetic factors.

Recently, Yu *et al*. explored the function of XIST, a long non-coding RNA, which is essential for X chromosome inactivation in female cells in the early stages of development. In adult B cells, XIST plays an important role in the regulation of X-linked immune genes such as TLR7. Through the analysis of single-cell transcriptome data from female patients affected by SLE or COVID-19 infection, XIST and XIST-dependent genes (including TLR7) were found to be dysregulated. An important consequence of TLR7 agonism, due to XIST inactivation, is the promotion of isotype-switching CD11c+ cells, atypical memory B cells (ABCs); this unique B cell population gained an important role in aging, infectious diseases and female-biased autoimmunity (4, 5). Thanks to these findings XIST seems to have a growing role in sex-related pathophysiological differences in SLE and in other diseases (6).

Another interesting study published during the last year was focused on genetic and epigenetic regulations of B cells activity in SLE; Pyfrom *et al*. profiled the epigenetic features of inactive X chromosome (Xi) in human B cell subsets from paediatric and adult SLE patients compared to healthy controls through RNA fluorescence in situ hybridation and immunofluorescence. The results revealed an aberrant X-linked gene expression form the Xi in human SLE B cells, suggesting an important contribute of X-linked gene expression on female bias in SLE (7).

During 2021, several studies were focused on different cytokines pathways in SLE, analyzing cytokine expression levels in different biological samples from SLE patients, trying to suggest

possible new targets for therapies. In a recent paper, Peng *et al*. examined tear samples from patients affected by Sjögren syndrome (SS) and SLE with established dry eye syndrome (DE), analysing T-helper 17 (Th17) cell-related cytokines, including interleukin (IL)-1b, IL-2, IL-4, interferon (IFN)-y, IL-6, IL-8, IL-17F, tumour necrosis factor (TNF)-α, IL-21, IL-22, and IL-23. Cytokines levels in these patients were assessed and compared with healthy controls and patients with non-specific dry eye disease. The study showed abnormal regulation of Th17 expression pathway in SLE and SS patients, suggesting a pathogenetic role in DE. Particularly Th17 related cytokines, such as IL-8 and IL-21 may become a potential therapeutic target in SLE and SS DE (8).

The pathogenesis of articular involvement in SLE is also unclear. A recent study explored cytokines pathways in SLE arthritis, assessing cytokines expression level and cellular composition in synovial fluids of SLE patients, excluding the presence of comorbidities such as osteoarthritis or overlap with rheumatoid arthritis. IL-17a and IL-6 levels were found to be high in SLE synovial fluid, as well as a subset of the synovial $CD4^+$ T cells expressing $CCR6^+$, a marker associated with Th-17 pathway. These data suggest a potential implication of Th17 cytokine pathway in pathogenesis of lupus arthritis (9).

Other cytokine pathways potentially involved in SLE pathogenesis have been explored in recent studies. A meta-analysis was focused on the association between circulating level of IL-18 and SLE. The results showed a significantly higher level of circulating IL-18 in SLE patients in comparison with healthy controls, especially in patients with higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, Asian, European, Arab or mixed ethnicity, suggesting an underlying pathogenetic role of IL-18 in SLE (10). Likewise, Ma *et al*., investigated the role of IL-18 and IL-18 receptor accessory protein (IL18RAP) as neutrophils-driving cytokine. In neutrophils from SLE patients, particularly those with a history of renal involvement or high disease activity, elevated expression of IL18RAP was found. Moreover, neutrophils showed higher IL-18-mediated enhancement in activity by reactive oxygen species production and could be neutralised by anti-IL18RAP blocking antibodies. These data reveal that IL-18 likely contribute to SLE pathogenesis through mediation of neutrophil dysfunction via the upregulation of IL18RAP expression (11).

Take home messages on pathogenesis

- New evidences suggest that sex-bias in SLE is likely related to epigenetically-induced modifications in X-linked immunity genes expression, especially in B cells-driven autoimmunity (4-7);
- the T helper 17 (Th17) pathway has been implicated in several aspects of SLE disease pathogenesis (8, 9);
- IL-18 is confirmed to have a recognised role in SLE disease progression and activity (10, 11).

Biomarkers

To date, only few biomarkers for SLE are validated and used in clinical practice, but many are under investigation for early diagnosis and disease monitoring.

Yang and *et al*. recently analysed transfer RNA (tRNA)-derived small non-coding RNA (tsRNA) signatures in the serum of 192 SLE patients and 109 controls. tRF-His-GTG-1 was significantly upregulated in SLE and, in combination with anti-dsDNA, allowed a fairly good discrimination between SLE patients and controls (12).

The Zeus study group (13) determined the serum levels of five antibodies of IgG2 isotype, namely anti-dsDNA, anti-H2/H3, anti-C1q, anti-αENO and ANXA1, in 1052 SLE patients with lupus nephritis (LN). The full panel was highly discriminatory between SLE/LN patients and healthy subjects. Additionally, anti-H2A, anti-ANXA1 and anti-dsDNA were able to discriminate between SLE/LN and other rheumatologic conditions; anti–ENO1 and anti-H2 IgG2 were specific for the LN subgroup and their levels had a positive correlation with SLEDAI.

Khadjinova and colleagues (14) investigated the presence of recombinant envelope (Env) protein and anti-human endogenous retrovirus K (HERV-K) Env autoantibodies in the serum of SLE patients and of control patients. The results showed that patients with SLE had a higher titre of anti-HERV-K Env autoantibodies in comparison with healthy controls and patients with other rheumatic conditions.

Dias and colleagues (15) explored possible correlations between SLE disease activity and some neurotrophic factors, responsible not only for neuronal function but also for immune system modulation. Brain-derived neurotrophic factor (BDNF), neurotrophic factor-3 (NT-3), neurotrophic factor-4 (NT-4), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) levels were measured in plasma from 34 SLE patients and 34 healthy controls. GDNF, NGF, NT-4 and BDNF plasma levels were significantly lower in SLE patients than in controls, and lower levels of GDNF and BDNF correlated with more severe disease. To explain these findings, it was speculated that prolonged inflammatory conditions like SLE may decrease the production of neurotrophic factors. Nevertheless, SLE patients had a higher rate of depression (29%) compared to matched controls (0%), and psychiatric comorbidity could be a potential confounding factor.

Moreau *et al*. (16) observed that seric interleukin 33 (IL-33) and soluble ST2 (sST2) levels were significantly higher in SLE patients compared with controls. Moreover, sST2 levels were significantly higher in patients with LN and significantly correlated with SLEDAI. In renal biopsies no differences were found in IL-33 immunoreactivity, while sST2L expression was significantly higher in patients with LN compared with controls.

In another case-control study involving 200 female SLE patients and age, sex, matched healthy controls, CD14 (C-159T) polymorphism was associated with an increased predisposition to the development of SLE and LN, and soluble CD14 (sCD14) levels had a positive correlation with SLEDAI-

2K scores and 24 hours proteinuria, representing a potential biomarker of disease activity (17).

To date, renal biopsy represents the gold standard for the diagnosis and classification of nephritis. However, there is an increasing interest in serum and urinary biomarkers to find a less invasive alternative for monitoring and predicting treatment response. Among potential biomarkers, we find tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), a TNF superfamily cytokine that is frequently up-regulated in the blood and urine from patients with active LN. In a recent metanalysis (18) the overall pooled sensitivity of TWEAK was 0.69, the specificity was 0.77. The overall pooled positive likelihood ratio (LR) was 3.31 and the negative LR 0.38.

In a recent study, Yu *et al*. (19) observed that seric syndecan-1, hyaluronan (HA) and thrombomodulin levels were significantly higher during active LN compared with remission. Syndecan-1 was highly effective in discriminating between active LN, healthy subjects, patients with non-lupus chronic kidney disease and inactive LN, while it was less specific in distinguishing active renal and non-renal involvement. Thrombomodulin enabled a good discrimination between active LN, healthy subjects and active non-renal lupus, but it was less useful in discriminating active LN from non-lupus chronic kidney disease. HA distinguished quite well active LN from healthy subjects, LN patients in remission and non-lupus chronic kidney disease, but it did not discriminate between renal and non-renal lupus. In kidney biopsies, syndecan-1 and thrombomodulin levels correlated with the severity of interstitial inflammation, while HA levels correlated with chronicity grading. Moreover, longitudinal studies showed that HA levels ran in parallel with LN activity, increasing at the time of nephritic flare, and decreasing with treatment response. Conversely, syndecan-1 and thrombomodulin increased 3.6 months before the clinical renal flare, and they can therefore be regarded as potential early biomarkers of renal involvement.

Davies *et al*. (20) collected urine samples from 197 SLE patients (75 with active renal involvement) and 48 healthy controls and measured the concentration of a urinary panel of proteins. The combination of lipocalin-like prostaglandin D synthase (LPGDS), transferrin, ceruloplasmin, monocyte chemoattractant protein 1 (MCP-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) was a good predictor of active LN. Moreover, a combination of LPGDS, transferrin, AGP-1 (alpha-1-acid glycoprotein), ceruloplasmin, MCP-1 and sVCAM-1 predicted good response to rituximab (RTX) treatment at 12 months.

Sometimes it is difficult to establish if a persistent proteinuria is due to kidney damage or chronically active/refractory nephritis. As observed by Mejia-Vilet *et al*. (21), urinary epidermal growth factor (EGF) was significantly lower in patients with active LN compared to that in patients with active nonrenal SLE, inactive SLE, and healthy kidney donors. Moreover, the urinary EGF level was inversely correlated with the chronicity index in kidney biopsy, and lower urinary EGF levels at the time of flare are associated with adverse long-term kidney outcomes.

Active SLE is associated with a higher risk of thromboembolism, especially (but not exclusively) in the presence of antiphospholipid (aPL) antibodies. As proposed by Ramirez *et al*., anti-protein C antibodies (anti-PC) might prove to be a novel marker to monitor this potentially life-threatening risk. They performed a cross-sectional study of 156 SLE; anti-PC positivity was detected in 54.5% of patients and was significantly associate with acquired Protein C Resistance (APCR); moreover, high-avidity anti-PC positivity (26.3% of patients) was significantly associated with thrombosis and active disease (22).

Among cardiovascular risk factors, diabetes is certainly a daunting comorbidity in SLE. To investigate insulin resistance in SLE, Martín-González and colleagues analysed the expression of Apolipoprotein C3 (ApoC3) in a cohort of 140 non-diabetic patients with SLE. As in the general population, ApoC3 was linked to pancreatic beta-cell impairment (23)

Another recent study on this topic (24) demonstrated that serum amylin, a pancreatic hormone involved in glucose homeostasis, was significantly higher in non-diabetic SLE patients compared to controls, especially in patients with higher disease severity and damage. Multivariate analysis suggested this upregulation to be independent from prednisone administration.

In another recent paper, Hernandez-Molina *et al* .(25) investigated T follicular helper cell (Tfh) profile in minor salivary gland (MSG) biopsies from a small cohort of patients with primary SS (pSS), SLE/SS, SLE and non-SS sicca. In pSS there was a higher expression of Tfh1, Tfh2, and Tfh17 cells; conversely, Tfh17 and Tfh1 cells were predominant in SLE/SS and SLE patients, respectively.

Take home messages on biomarkers

- tRF-His-GTG-1, IgG2 isotype antibody panel and anti- human endogenous retrovirus K envelope autoantibodies seems to be potential diagnostic biomarkers (12-14);
- neurotrophic factors, IL-33, soluble ST2 and soluble CD14 are potential biomarkers for disease monitoring (15-17);
- potential biomarkers for active lupus nephritis include: seric syndecan-1, hyaluronan and thrombomodulin; urinary EGF; combination of urinary lipocalin-like prostaglandin D synthase, transferrin, ceruloplasmin, MCP-1 and sVCAM-1 (19-21);
- apolipoprotein C3 and amylin are biomarkers for insulin resistance, and anti-protein C antibodies increase thromboembolic risk (22-24).

Clinical manifestations and comorbidities

In the neuropsychiatric (NP) field, Hanly *et al*. further advance the understanding of the outcome of nervous system manifestations in SLE patients identifying the variables associated with the development and resolution of NP events over time (26). Over 12 years (1999–2011), 1.827 patients were recruited into the Systemic Lupus International Collaborating Clinics

(SLICC) prospective inception cohort for a total of 1.910 NP events (52.3%), of these 593 (31.0%) attributed to SLE. Factors associated with the onset of NP events attributed to SLE were male sex, concurrent NP events not attributed to SLE and excluding headache, SLEDAI-2K without NP variables and glucocorticoid use (26). Conversely, there was a negative association with Asian race, postsecondary education and antimalarial drug use. NP events attributed to SLE had a higher resolution rate than NP manifestations not attributed to SLE. Factors associated with the resolution of NP events attributed to the diseases were the Asian race and any central/focal NP event (26).

Attributing NP manifestations to SLE is often challenging. Brain white matter (WM) lesions are frequent in SLE at MRI, but their diagnostic role is unclear. Ramirez *et al*. assessed whether WM lesions count, volume and distribution measurement can help in the diagnosis of NPSLE (27). Patients with NPSLE had higher WM lesions volume than patients without NP involvement and healthy controls. Thresholds of WM hyperintense WM lesion volume ≥0.423 cm3 or ≥12 were associated with definite NPSLE and improved the classification of patients with possible NPSLE according to clinical judgment (27). Interestingly, a pilot study investigated WM microstructural changes in newly diagnosed SLE patients, even in the absence of clinically manifested NP events. Evaluating the longitudinal variations in diffusion tensor imaging (DTI) metrics of different WM tracts the authors observed that mean diffusivity (expression of the motion of water molecules within the tissue, sensitive to cellularity, oedema) and radial diffusivity (a parameter sensitive to changes in axonal diameter and density due to demyelination as well as other perturbations that may affect the interstitial space) significantly increased over time (28). These findings suggest that the deterioration of the integrity of WM starts in the early phases of the SLE course and calls for better monitoring of WM tissue.

LN is another major organ involvement described approximately in 50% of patients with SLE that can progress to end-stage renal disease in 10% of the case. Prediction of outcomes at the time of LN diagnosis can guide decisions regarding intensity of monitoring and therapy for treatment response. In this view, a combination of renal pathology results and routine clinical laboratory data was used to develop and to cross-validate a clinically meaningful machine learning decision tool able to predict LN outcomes at approximately 1 year. A report provided, for the first time, five different machine learning models based on the inclusion of seven predictors that were interstitial inflammation, interstitial fibrosis, activity score and chronicity score from renal pathology and urine protein to creatinine ratio, white blood cell count and haemoglobin from the clinical laboratories (29).

Still in the framework of renal function, Yip *et al*. characterised the longitudinal variation of estimated glomerular filtration rate (eGFR) in the Hopkins Lupus Cohort identifying three different states: declining (<4 mL/min/1.73m^2 per year), stable (<4 to 4mL/min/1.73 m^2 per year) and increasing (>4mL/min/1.73 m^2 per year) states. In adjusted analyses, high blood pressure, C4 and low haematocrit were associated with a change from non-declining to declining state. High urine protein-to-creatinine ratio also tended to be associated with a change from non-declining to declining state, while the use of prednisone stabilises the declining eGFR trajectory (30). Regarding end-stage renal disease related to LN, a retrospective study evaluated the long-term post-transplant graft and patient survival in LN compared to patients with polycystic kidney disease (31). In total, 53 kidney transplanted patients were included, 21 in the LN group and 32 in the polycystic kidney disease group. No significant differences were found regarding graft or patient survival at 20 years of follow-up (31). Finally, a retrospective study characterised predictors of chronic damage accrual and mortality in LN over 18 years of observation. At multivariate analysis, high blood pressure, presentation with acute renal dysfunction and average prednisone dose >5mg/day independently predicted damage. Age, hypertension, and maintenance therapy with immunosuppressants predicted mortality (32).

SLE is associated with considerable morbidity and mortality. A recent analysis conducted a population-based cohort study containing computerised medical records of 10 million patients, representing 8% of the British population, estimated the risk of mortality in 4.343 patients with SLE compared with 21.780 matched controls (33). SLE conferred a 1.8-fold increased mortality rate for all-cause compared with matched subjects. The age-specific mortality risk was highest in patients aged 18–39 years. After adjustment for potential confounders (history of seizures, renal disease, and recent use of glucocorticoids (GCs), antimalarials or antidiabetics), mortality rates for cardiovascular disease, infectious disease, non-infectious respiratory disease and death attributable to accidents or suicide were all significantly increased in SLE patients compared with matched controls, whereas the mortality rate for cancer was reduced (33).

Malignancy is potential comorbidity in patients with SLE. Clarke *et al*. elucidated the risk of malignancy type in SLE patients performing a systematic review and meta-analysis. Forty-one studies reporting on 40 malignancies (one overall, 39 site-specific) were included (34). The pooled risk ratio (RR) for all malignancies from 3.694 events across 80.833 patients was 1.18. The authors identified 24 site-specific malignancies with increased risk, including reproductive cancers (cervical, vagina/vulva), all haematologic cancers, all liver and hepatobiliary cancers, all respiratory cancers, stomach, oesophagus, colon and anal cancers and other cancers (bladder, thyroid, brain and nervous system) (34). For 11 site-specific malignancies including all gynaecologic and ovarian, gastrointestinal cancers (pancreas, colorectal, all gastrointestinal, rectal, oral, small intestine), skin cancer (non-melanoma, all skin), and kidney cancer there was no evidence of increased risk. A decreased risk was reported for breast, uterine, melanoma, and prostate cancers (34).

Novel data from a large, multicentre inception SLE cohort explored how

different cancer types in SLE could be associated with specific risk factors (35). In this study, multivariate analyses indicated that overall cancer risk was related primarily to male sex and older age at SLE diagnosis. In addition, smoking was associated with lung cancer. Immunosuppressive medications were not associated with higher risk except for cyclophosphamide (CYC) and non-melanoma skin cancer. Antimalarials were negatively associated with breast cancer and nonmelanoma skin cancer risk. SLE activity was associated positively with hematologic cancer and negatively with nonmelanoma skin cancer (35).

With regards to infection, a nationwide study examined the time trends and outcomes of 5 common hospitalised infections in patients with SLE, namely, pneumonia, sepsis/bacteraemia, urinary tract infection, skin and soft tissue infections, and opportunistic infections (36). The rates of hospitalised infections increased over time from 1998 to 2016 patients with SLE, and sepsis surpassed pneumonia as the most common hospitalised infection. SLE patients hospitalised for one of the five included infections were younger in age (median age lower by 13 years), were more likely to be female and to be in the lowest income quartile compared with non-SLE patients (36).

Take home messages on clinical manifestations and comorbidities:

- Neuropsychiatric (NP) events attributed to SLE have a higher resolution rate than NP manifestations not attributed to SLE. The resolution is more common in patients of Asian race and for central/focal NP manifestations (26);
- in lupus nephritis, presentation with acute renal dysfunction, presence of arterial hypertension and corticosteroids dose independently predict damage increase over time (32);
- SLE is associated with a 1.8-fold increased mortality rate for all-cause mortality (33);
- the rates of hospitalised infections are increasing over time in patients with SLE, and sepsis is the most common hospitalised infection (36).

Therapy

New potential therapeutic targets: phase I and II studies

New insights in the pathogenesis of SLE and advances in biotechnology provided new potential therapeutic targets.

In 2021, tyrosin kinase inhibitors have been investigated as potential treatment targets for SLE patients. Hasni *et al*. (37) reported the results of the phase 1 randomised, double-blind, placebo-controlled trial with tofacitinib. In this study 30 SLE patients were randomised to tofacitinib (5 mg twice daily) or placebo in 2:1 block. Tofacitinib was found to have a good safety profile in SLE and the study showed that tofacitinib improves cardiometabolic profile with possible role in preventing atherosclerosis in SLE patients.

A phase II, randomised, double-blind, placebo-controlled trial was recently conducted to assess safety and efficacy of fenebrutinib (GDC-0853), a non-covalent, oral, and highly selective inhibitor of Bruton's tyrosine kinase (BTK). Two hundred and sixty patients with SLE were randomised to receive placebo, fenebrutinib 150 mg once daily, or fenebrutinib 200 mg twice daily. The results showed that fenebrutinib is safe but its efficacy, evaluated with SRI-4, was not demonstrated (38).

Furie *et al*. (39) assessed efficacy and safety of dapirolizumab pegol (DZP), a polyethylene glycol-conjugated Fab' fragment, which targets CD40 ligand performing a phase 2, 24-week, randomised, placebo-controlled trial including 182 patients. Randomised patients received placebo or intravenous DZP (6/24/45 mg/kg) and standard-of-care (SOC) treatment every 4 weeks to week 24. After 24 weeks, DZP appeared to be well tolerated and an improvement of clinical and immunological parameters of disease activity was observed.

For the first time a phase IIa, open-label, dose-escalating study investigated safety and efficacy of a short course of intravenous arsenic trioxide (ATO) in 10 patients with active SLE. ATO was administered with 10 intravenous infusions within 24 days; the first group received 0.10 mg/kg per injection, with dose-escalating to 0.15 mg/kg in a second group, and to 0.20 mg/kg in a third group. An acceptable safety and efficacy of ATO were observed (40).

The type I IFN system is known to play a central role in the pathogenesis of SLE. Anifrolumab is a fully human monoclonal antibody that inhibits activity of all type I IFNs. Recently, a 3-year, phase II open-label extension study confirmed that anifrolumab had an acceptable safety profile in the long-term. Specifically, in the study 218 (88.6%) of the 246 patients who completed treatment in the MUSE phase IIb randomised controlled trial (41) are enrolled; 139 (63.8%) completed 3 years of treatment. About 70% of patients reported at least one adverse event (AE) during the first year of the extension study and about 7% stopped treatment due to AEs. During 3 years of follow-up improvement of SLE disease activity, quality of life and serologic measures were sustained (42).

Combination therapies are also one of the new frontiers in the management of SLE and they have been explored in recent studies. In particular, over the last year encouraging results have been obtained by combination therapy with RTX and belimumab. In this regard, in an American multicenter, phase II randomised, open-label clinical trial 43 patients with recurrent or refractory LN were treated with RTX, CYC, and GCs, followed by weekly belimumab infusions until week 48 or treated with RTX, CYC and GCs alone. The results showed that the addition of belimumab to RTX and CYC did not increase incidence of AEs; moreover, in patients treated with belimumab lower maturation of transitional to naive B cells was observed as well as higher negative selection of autoreactive B cells (43). In another phase 2, randomised, double-blind, placebo-controlled, parallel-group, superiority trial, 52 patients were treated with RTX and 4 to 8 weeks later were randomly assigned (1:1) to receive intravenous belimumab or placebo for 52 weeks. At 52 week combination therapy significantly reduced serum anti-dsDNA antibody levels and reduced risk for severe flare in patients with SLE that was refractory to conventional therapy (44).

Another B-cell targeted therapy is ataci-

cept, a human recombinant fusion protein directed both to BLyS and APRIL. In 2021, the long-term extension (LTE) study of ADDRESS II was published, in this study Wallace *et al*. (45) included 253 patients whose 88 received atacicept 150 mg, 82 atacicept 75 mg and 83 placebo/atacicept 150 mg; median treatment duration was 83.8 weeks; the study confirmed efficacy and safety of atacicept 150 mg also in the long-term.

Piranavan *et al*. described the outcome of 73 SLE patients treated with sirolimus for more than 3 months. Twelve patients were treated for renal manifestations, while 61 for non-renal manifestations. In both groups sirolimus led to good results in disease activity control and in steroid reducing, with good tolerability profile also in long-term use. In the renal group, sirolimus was administered in cases of intolerance or inadequate response to MMF, while in non-renal patients sirolimus was used to treat uncontrolled musculoskeletal, mucocutaneous, NP, serositic and haematological manifestations despite the use of at least two "disease modifying antirheumatic drugs" (DMARDs) (46).

Data of safety and efficacy of bortezomib (BTZ) in SLE patients who did not respond to conventional immunosuppressive agents was reported by Walhelm *et al*. This drug is a specific, reversible, inhibitor of the 20S subunit of the proteasome and it was administrated in combination with GCs. Despite the low number of cases (12 patients), BTZ caused reduction in SLEDAI, which was maintained at 6 and 12 months, increase in complement levels, reduction of proteinuria and seroconversion of anti-dsDNA. AEs were recorded in 6 patients and the most common were infections, underling the need to take care of hypogammaglobinaemia (47).

Take home messages on new potential therapeutic targets

- Combination therapy with rituximab and belimumab seems to be promising treatment for refractory patients with good safety profile (44);
- in extension of phase II studies both anifrolumab and atacicept demonstrated acceptable safety for also for long period of treatment (42, 45).

New perspectives on traditional drugs

Despite new treatment strategies, GCs remain of pivotal importance in the treatment of SLE and are used to treat severe disease manifestations as well as in the long-term as maintenance therapy. Data from patients with 2 consecutive years of clinically quiescent disease were analysed to assess if gradual tapering of GCs was associated with different rates of clinical flare and damage accrual in comparison to low dose (5 mg/day) prednisone maintenance therapy. All patients (n=102 in each group) were followed for 2 years. Flare rate was lower in the withdrawal group both at 12 (17.6% *vs*. 29.4) and 24 months (33.3% *vs*. 50%), and damage accrual was less frequent in the withdrawal group. So, the study suggest that GCs withdrawal is feasible in patients with clinically quiescent SLE and it is not related to a significant incidence of flare (48).

Argolini *et al*. have recently analyzed data from 106 patients to investigate the outcome of LN patients on long-term maintenance therapy with cyclosporine (CsA), mycophenolate mofetil (MMF) or azathioprine (AZA). All treatments had similar efficacy in achieving and maintaining complete renal remission at 1 and 8 years, with similar 24 h proteinuria, serum creatinine, and eGFR. Flares-free survival curves and incidence of side-effects were not significantly different in the three groups. Interestingly, at the beginning of maintenance therapy, CsA patients had significantly higher proteinuria or nephrotic syndrome and significantly lower complete renal remission with respect to the other groups (49).

With regards to MMF, a longitudinal observational study was recently carried out in 162 SLE patients to evaluate the 5-years drug retention rate (DRR) and its effectiveness to control chronic damage progression. Most patients (62.3%) were assuming MMF for LN, while 24.1% were treated for musculoskeletal manifestations. The median treatment duration was 30 months, and at 60 months follow up the DRR was similar between LN patients and patients treated for other indications, with higher DRR when MMF was used to treat joint manifestations. During the follow up period about 20% of patients discontinued MMF for AEs and 21.7% for achieving remission. Also, the median SLICC Damage Index (SDI) values didn't significantly increase. These results suggest that MMF is able to control chronic damage progression and is effective also in non-renal involvement, particularly in musculoskeletal involvement (50).

New data on calcineurin inhibitors

Recently, growing interest has been raised for calcineurin inhibitors, especially in patients who do not achieve complete renal response to standard treatments.

Tacrolimus, a calcineurin inhibitor, is considered as a promising treatment option for LN. A study on long term-safety and effectiveness of this drug in 1355 Japanese patients has recently provided interesting results. In this large population of patients with LN, long-term tacrolimus maintenance treatment over 5 years was well tolerated and effective. The most frequent adverse drug reactions were infections, which generally developed early in the treatment period (51).

Voclosporin is a novel calcineurin inhibitors developed for the treatment of LN, and a phase 3, multicentre, double-blind, randomised trial was recently carried out to determine the complete renal response at week 52 in voclosporin-treated patients (n=179) *versus* a placebo group (n=178). All patients were also receiving MMF and low-dose GCs. In the voclosporin group, patients achieved a significantly higher complete renal response rate at 1 year compared to patients receiving MMF and low-dose GCs alone. Safety profile was comparable in the two groups, suggesting voclosporin as an opportunity in patients with LN (52).

New data on biotechnological drugs – Belimumab

Since belimumab approval, many data have been collected about the efficacy and safety of this drug from long-term extension studies and real-life.

The results of a *post-hoc* analysis of 448 patients enrolled in Belimumab

International Study in LN (BLISS-LN) was recently published by Rovin *et al*. Patients were randomised to receive intravenous belimumab10 mg/kg or placebo, and the results showed that add-on belimumab on standard therapy could facilitate control of disease activity, prevent LN flares, and help to preserve long-term kidney function (53).

The results of the EMBRACE study, a 52-week double blind placebo-controlled trial in 448 adult patients of self-identified black race with active SLE, were described by Ginzler *et al*. The primary endopoint, SLE Responder Index–SLEDAI-2K (SRI-S2K) response rate at week 52, was not achieved in these patients who were receiving monthly intravenous belimumab 10 mg/kg or placebo in addition to standard therapy. However, SRI-S2K response rates were higher in belimumab group, especially in patients with high baseline disease activity or renal manifestations (54).

Gatto *et al*. reported results of an analysis of 91 SLE patients with renal involvement enrolled in

the BeRLiSS (Belimumab in Real Life Setting Study) and evaluated at 6, 12 and 24 months. The data confirmed that add-on therapy with belimumab led to durable renal response in 70.3% of these patients, who achieved proteinuria ≤0.7 g/24 h and eGFR≥60 ml/min/1.73 m^2 without rescue therapy in a real-life setting. Also, 38.4% of them had complete renal response with proteinuria <0.5 g/24 h and eGFR≥90 ml/min/1.73 m^2 (55).

– Others

Anifrolumab resulted an important treatment option in moderate to severe SLE patients and could help to taper GCs. TULIP-1 and TULIP-2 were phase 3, 52-week trails in which patients were randomised to receive intravenous anifrolumab (300 mg every 4 weeks for 48 weeks) or placebo. In patients who were receiving baseline GCs (10 mg/day prednisone or equivalent) tapering to 7.5 mg/day from weeks 8–40 was required. A *post-hoc* analysis of data from these trials has shown that patients under anifrolumab treatment (n=360) developed fewer flares and had a prolonged time to first flare versus patients in the placebo group (n=366), and this result was confirmed also in patients who tapered GCs (56).

Take home messages on new therapies and therapeutic strategies

- Glucocorticoids tapering and withdrawal can be safe in patients with clinically quiescent SLE (48);
- belimumab can be considered as an add-on therapy for adult patients with active lupus nephritis (53-55), and also data on calcineurin inhibitors (voclosporin and tacrolimus) show promising results in renal involvement (51, 52);
- in patients with lupus nephritis maintenance therapy with cyclosporine, mycophenolate mofetil or azathioprine had similar efficacy in achieving and maintaining complete renal remission at 1 and 8 years (49).

Treat-to-target, remission, LLDAS, patient-reported outcomes

Although several years have passed since when the strategy of "treat to target" has been applied in SLE (57), the optimal approach for the treatment of the disease remains uncertain. The Definitions Of Remission In SLE (DORIS) initiative was started in order to provide a framework for defining remission as the ideal target of SLE management. The first results of this initiative were published in 2016 (58). In 2020, the task force was reconvened and, on the basis of systematic literature reviews and data from individual cohorts and registries, achieved consensus on the 2021 DORIS definition of remission in SLE which includes: clinical SLEDAI=0 and Physician Global Assessment (PhGA) <0.5, irrespective of serology; the patient may be on antimalarials, low-dose GCs (prednisolone <5 mg/day), and/or stable immunosuppressives including biologics. In detail, the task force defined some general recommendations: inclusion of serology and duration in the DORIS definition of remission is not recommended; the SLEDAI-based definitions of remission have been investigated more extensively than BILAG- or ECLAM-based definitions, therefore the SLEDAI-based definitions can more confidently be recommended; the definition of remission off-treatment is not recommended for clinical research or clinical trials as it is achieved very rarely (59).

It is thought that this single definition of remission in SLE should represent an aspirational goal in clinical care and an outcome in research, however it seems that the ideal target of the management of SLE has not yet been found. Mucke and co-workers evaluated the agreement of the DORIS definition of remission with the treating physician's (DORIS-) independent remission judgement in a monocentric SLE cohort and they found a discordance regarding DORIS remission and the physician's judgement in 22.7% of cases, with a greater number of patients considered in remission by their physicians (60).

Indeed, the literature in the last year has been characterised by studies focused on the proposal of new targets for the treatment in SLE.

SLE Disease Activity Score (SLE-DAS) is a novel, rapid and continuous score with improved sensitivity to change as compared with the SLEDAI-2K by weighing some domains like joint count, proteinuria and the hematological manifestations. In the last year, the Padua and the Cochin Lupus clinics have derived and validated the SLE-DAS definitions for disease activity categories and clinical remission state. The SLE-DAS cut-offs were derived in Padua cohort: remission, SLE-DAS ≤2.08; mild activity, 2.08<SLE-DAS ≤7.64; moderate/severe activity, SLE-DAS >7.64. Its performance was assessed against expert classification in Cochin cohort and BILAG index in BLISS-76: sensitivity and specificity resulted above 90%, 82% and 95% for remission, mild and moderate/severe activity, respectively (61).

Abdelhady *et al*. has also explored the validity of the SLE-DAS index for the definition of Lupus Low Disease Activity State (LLDAS). In a group of 117 SLE patients they found a good agreement between SLEDAI-2K-derived definition of LLDAS and SLE-DAS definition, identifying a SLE-DAS cut-off of 6.62 for the definition of LLDAS (62).

Touma *et al*. has recently evaluated

the performance of the SLEDAI-2KG (SLEDAI-2K Glucocorticoids) index which adds one additional variable (GCs dosage) to the SLEDAI-2K. In a cohort of 188 SLE patients from the Toronto Lupus Clinic, response to standard of care therapy at first follow-up visit was assessed using the SLEDAI-2K and SLEDAI-2KG and the performances of the two indices were compared. The SLEDAI-2KG identified 97.9% responders among the SLEDAI-2K responders. More importantly, the SLEDAI-2KG identified 11 (25.6%) additional responders among SLEDAI-2K non-responders thanks to its ability to account for the decrease in GCs dose (63).

Ceccarelli *et al*. have recently proposed the Lupus comprehensive disease control (LupusCDC) as a unique outcome for the evaluation of SLE patients. It was defined as remission achievement for at least one year plus absence of chronic damage progression in the previous one year. In their longitudinal analysis, including 172 patients with 5-years follow-up and at least one visit per year, they found that the failure to reach this condition was significantly associated with renal involvement and with the intake of immunosuppressant drugs and GCs (64).

Effective treatment strategies to control disease activity and prevent flares are important to improve patients' perception of their health status. It has been demonstrated that flaring SLE patients have worse Patient Reported Outcomes (PROs) (65), however, there is no linear correlation between a good control of disease activity and the improvement of patients' Health Related Quality of Life (HRQoL).

Actually, all "treat to target" definitions are based on validated clinician-assessed instruments, while PROs are not included. Therefore, patients and physicians may have different expectations of remission and low disease activity states, which may ultimately lead to the failure to improve patients' HRQoL and to patients' dissatisfaction with treatment (66).

In a recent study by Sloan *et al*., conducted with a mixed methodology involving thematic analysis of in-depth interviews to further explore quantitative survey findings, satisfaction with medical care was significantly lower for non-adherent patients and for those not reporting non-adherence to their physicians, particularly in relation to support, information and physician's listening skills. Moreover, the immediate effect on symptom control and improving QoL was the most frequently cited reason for medication adherence, whereas preventing organ damage and/or death -which represent physicians' main goals- was only cited by <10% of participants (67).

In this regard, Gomez *et al*. have recently determined the prevalence of adverse HRQoL outcomes (SF-36 scale scores ≤ the 5th percentile derived from age- and sex-matched population-based norms, and FACIT-Fatigue scores <30) in patients with SLE who met the primary endpoint of the BLISS-52 and BLISS-76 trials and identified contributing factors. They found a high frequency of adverse HRQoL outcomes, despite adequate clinical response to standard therapy plus belimumab or placebo, the highest in SF-36 general health (29.1%), followed by FACIT-Fatigue (25.8%) and SF-36 physical functioning (25.4%). While no impact was documented for disease activity, established organ damage contributed to adverse outcome within physical HRQoL aspects and add-on belimumab was shown to be protective against adverse physical functioning and severe fatigue (68).

Actually, fatigue confirms to be one of the most burdensome symptoms for patients with SLE. Lupus Europe, a major European lupus patient association, has performed a survey about the impact of SLE in Europe from the patient perspective, involving a large sample of 4375 respondents from 35 European countries who reported having physician-confirmed SLE. Fatigue was the most common reported symptom (85.3%) and the main three symptoms that respondents would like the most to go away were "fatigue and weakness" (55.1%), joint (49.5%) and muscle (33.4%) pain. Moreover, 16.7% identified anxiety or depression as one of their most bothersome symptoms. Almost half of respondents declared that the disease had a medium, high or very high impact on their ability to perform normal daily activities (69).

Similar findings also emerged from the analysis of factors detrimental to work productivity in the German LuLa study, a longitudinal patient-reported study. The authors found that impaired work productivity and impaired daily activities were frequently reported among employed SLE patients (almost 20–30%) and that fatigue, disease activity and pain had a synergistic detrimental effect (70).

In the last year, the results of an online survey of adult patients with SLE conducted in the US have also been published. The authors particularly focused on patients' satisfaction with treatment. As expected, fatigue, musculoskeletal pain and sleep disturbances were the most frequently reported symptoms (by more than half of respondents); reducing fatigue, pain and the frequency/severity of flares were the most common treatment goals reported as "very important" by participants. It is also important to note that 63% of respondents indicated that their healthcare provider had not asked them which were their most important treatment goals. Interestingly, survey participants did not consider the reduction of corticosteroid use a high priority of their treatment strategy (66).

Thus, it emerges the controversial relationship that patients with lupus have with chronic corticosteroid treatment: on one hand it seems that they are not fully aware of the potential risks associated with GCs long-term use and the importance of trying to reduce the doses; on the other hand, data from recent literature underline that chronic glucocorticoid therapy have a negative impact on patients' HRQoL. A study recently conducted in 10 Japanese institutions, in line with data of the previous year (71), have demonstrated that daily glucocorticoid doses are inversely associated with emotional health among SLE patients in LLDAS (72).

As already emerged in the survey conducted by Lupus Europe, mood disorders are frequent among patients with SLE and may negatively influence patients'

HRQoL. Cross-sectional data recently obtained from a cohort of 326 adults with SLE in the San Francisco Bay Area have confirmed that major depression is quite frequent in patients with lupus (almost 25% of participants) and is associated with markedly reduced HRQoL as measured by PROMIS. In particular, in this study depressed individuals presented worse scores on fatigue, sleep impairment, negative psychosocial impact of illness, satisfaction in discretionary social activities, and satisfaction in social roles (73).

Currently, most studies only use PROs as secondary endpoints and clinicians still prefer to focus on clinical or laboratory evidence, however evidence gained from actively listening to patients' priorities and individual treatment goals could build a more positive medical relationship and could also improve disease outcomes and reduce the significant psychosocial impact of SLE (67).

Take home messages on treat-to-target remission, LLDAS, patient reported outcomes

- The 2021 DORIS definition of remission in SLE has been published, however it seems that, from the clinician's perspective, the ideal treatment target for SLE has not yet been found (59, 60);
- patients and physicians may have different expectations of remission and low disease activity states: the improvement of fatigue, joint pain and quality of life appear to be the ideal treatment goals from the patient's perspective (66-71, 73).

SLE and COVID-19

During the last year, several studies have analysed the impact of coronavirus disease-2019 (COVID-19) and vaccine against severe acute respiratory coronavirus 2 (SARS-CoV-2) in SLE patients.

A recent systematic review (74) has identified only LN as predictor of severe to critical COVID19 in 48 COVID-19 SLE patients. None of the medications used to treat SLE was significantly associated with the severity of the COVID-19 infection, but patients with severe to critical COVID-19 were more likely to be treated with prednisolone (50% *vs*. 24%), although the difference was not statistically significant; no differences were found in age or disease duration between those with mild to moderate and severe to critical COVID-19.

Saxena *et al*. (75) analysed SARS-CoV-2 IgG antibodies in 329 SLE patients to provide data about efficacy and durability of humoral immunity and possible protection against re-infection with SARS-CoV-2. Patients were enrolled from the Web-based Assessment of Autoimmune, Immune-Mediated and Rheumatic Patients during the COVID-19 pandemic (WARCOV) study and the New York University (NYU) Lupus Cohort, and 29 patients had a history of COVID-19 confirmed by RT-PCR. The results showed that most patients with SLE and confirmed COVID-19 were able to produce and maintain a serological response despite the use of immunosuppressants, and the majority of them (70%) had antibody positivity beyond 30 weeks from COVID-19 onset.

Sjöwall *et al*. (76) have recently published data from 100 SLE patients obtained prior to the introduction of vaccines. Four patients (4%) had confirmed COVID19 during the study period, but 36% of the cohort had SARS-CoV-2 antibodies of ≥1 isotype. Interestingly, serological signs of exposure to SARS-CoV-2 seems to be poorly correlated to COVID19-related symptoms and seems to have a minor impact on SLE course. Additionally, GCs and DMARDs did not show any effects on the ability to mount an antibody response to SARS-CoV-2.

Another important finding emerged during the pandemic period was that treatment discontinuation seems to be an important cause of disease flare, suggesting that immunosuppressive treatment should not be preventatively discontinued in SLE patients. In an Italian cohort of 332 SLE patients 1.8% tested positive for SARS-CoV-2 infection with a mild course of the disease, and a significant correlation between flare and discontinuation of therapy (occurred in 11.1% and 8,1% of patients, respectively) was observed (77).

As concern vaccination, data from the international vaccination against COVID in systemic lupus (VACOLUP) study were recently published (78). All patients (n=696 from 30 countries) received at least one dose of vaccine, and almost half of patients also received a second dose; the most common vaccines were Pfizer-BioNTech, followed by Sinovac, AstraZeneca and Moderna. Flares occurred in 3% of patients with predominant musculoskeletal symptoms and fatigue, and no correlation with medications or previous SLE disease manifestations were observed. Side-effects after vaccination were recorded in around 50% of the cohort, but in most of cases did not impair daily functioning and did not depend from different type of vaccine. So, these results suggested that COVID19 vaccination was well tolerated in SLE patients.

Take home messages on SLE and COVID-19

- In SLE patients with COVID-19 only lupus nephritis resulted as a predictor of severe to critical COVID19, while none of the medications used to treat SLE was significantly associated with the severity of the COVID-19 infection (74);
- most patients with SLE and confirmed COVID-19 were able to produce and maintain a serological response despite the use of immunosuppressants (75);
- COVID-19 vaccination seems to be well tolerated in SLE patients (78).

Conclusion

During the last year many interesting data were published about SLE, and news regarding pathogenesis, clinical manifestations, therapeutic strategies and patients reported outcomes have been published. These data, which underline the growing interest in this complex disease, are summarised in this review.

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