Review

One year in review 2017: systemic lupus erythematosus

G.M.C. La Paglia[1], M.C. Leone[1], G. Lepri[2], R. Vagelli[3], E. Valentini[1], A. Alunno[1], C. Tani[3]

[1]*Rheumatology Unit, Department of Medicine, University of Perugia, Italy;*
[2]*Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Florence, Italy;*
[3]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy.*

Giuliana M.C. La Paglia, MD
Maria C. Leone, MD
Gemma Lepri, MD
Roberta Vagelli, MD
Eleonora Valentini, MD
Alessia Alunno, MD, PhD
Chiara Tani, MD, PhD

Please address correspondence to:
Dr Giuliana M.C. La Paglia,
Via dei Filosofi 43F,
06126 Perugia, Italy.
E-mail: lapaglia.giuliana@gmail.com

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominately affects women. It is characterised by a broad spectrum of clinical manifestations, however, its course and organ involvement are unpredictable. Although over the last few decades an improvement in survival for SLE patients has been observed, pathogenic mechanisms underlying this disease are still unclear. Comorbidities, due to both disease and treatment, as well as multiple aspects of SLE, are under intensive investigation. Following the previous annual reviews of this series, we hereby provide a critical digest of the recent papers on SLE focusing on pathogenesis, clinical and laboratory features, as well as current and new therapeutic strategies published over the last year.

Introduction

Following the previous papers of the "one year in review" collection on systemic lupus erythematosus (SLE) (1-2) we hereby provide an overview of the new insights in the pathogenesis, clinical and laboratory finding as well as treatment and comorbidities. We performed a MEDLINE search of English language articles published from 1st January to 31st December 2016 using MESH terms and free text words for the following search keys: systemic lupus erythematosus AND pathogenesis, clinical manifestations, comorbidities, biomarkers, therapy, phase III and post-marketing studies, registries, preclinical and phase I-II clinical studies. We reviewed all the articles and selected the most relevant papers. Only papers on adult SLE were considered.

Pathogenesis

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by an aberrant autoimmune response to self-antigens that can virtually affect any organs and tissues. The effects of environmental factors in genetically predisposed individuals, lead to the breaking of self-tolerance and to the activation/expansion of innate immune cells and autoreactive lymphocytes. Novel insights on SLE pathogenesis have been provided by animal models of the disease. With regard to lupus nephritis (LN), it has been demonstrated that the IL-17-interferon (IFN) type 1 interplay is crucial for the recruitment of immune cell to the kidney and the development of the inflammatory infiltrate as lupus-prone IL-17RA deficient mice develop a milder poly I:C-induced type I IFN-dependent glomerulonephritis (3). Furthermore, pristine-induced lupus in mice lacking of the newly defined Stat3-dependent Th17-specific regulatory T cells (Treg17) led to a worse clinical picture including LN (4). Among T lymphocytes, a peculiar subset characterised by the lack of CD4 and CD8 on the cell surface (double negative, DN) has been associated to SLE pathogenesis. Interestingly, DN T cells of mice lacking the chemokine receptor CXCR-5 and crossed with B6/lpr mice display a reduced migration into lymph nodes and kidneys (5). Impaired lysosomal maturation and, as consequence, reduced ability of lysosomes to degrade apoptotic debris within IgG immune complexes (ICs), has been observed in lupus-prone mice. This alteration fosters the accumulation of nuclear antigens and activates innate sensors that drive IFNα production (6). Furthermore, a wide range of phenotypic and functional abnormalities of plasmocytoid dendritic cells (pDCs) have been reported in several strains of lupus-prone mice. Since despite these differences all animals developed the

disease, this may suggest that the interaction with other immune cells rather than the features of DCs *per se* are the main determinant of disease development (7). Finally, a key role of IL-10 in curbing autoantibody production and supporting the expansion of innate-like lymphocytes including $CD5^+$ B cells and natural killer (NK) T cells (8).

Moving to the human counterpart, the identification of genetic factors associated to SLE susceptibility or to the development of specific autoantibodies or clinical feature is a topic under intense investigation (Table I) summarises the data published over the last year. As far as human leukocyte antigen (HLA) and related genes are concerned, DRB3, DRB4 and DRB5 do not change the risk of developing SLE (9) while single nucleotide polymorphisms (SNPs) of CFB, MICB and MSH5 increase SLE susceptibility (10-11).

A variety of non-HLA genes have emerged as possible candidates of genetic susceptibility to SLE but the majority of studies focused on specific ethnic groups thereby large scale data are rather few. Among the large family of cytokines, SNPs of IL-6, IL-10, IL12B, IL-17F, IL-31, IL-32 and IL-33 are associated with higher risk to develop SLE (12-17) but sursprisingly no association between IL-17A, a key player in SLE pathogenesis, has been observed (14). Furthermore, specific SNPs of the IL-27 genes are associated with reduced SLE risk (13) a SNP of the IL-17F gene is associated with the production of anti-double stranded (ds) DNA antibodies (14) and a SNP in the IL-19 gene is associated with LN (18), SNPs of several other molecules such as BLK, CCR5, ficolin, Fcγ receptors, MX1, PLA2R1, T-bet, TLR-9, TNF-α, TNFAIP3, the vitamin D receptor have been associated with higher risk of SLE (19-25) or LN (26-27) while data on PTPN22 are conflicting (28). Genome-wide association studies (GWAS) represent a step forward in the evaluation of gene abnormalities in several conditions including SLE. Two of such wide analyses have been conducted over the last year, one including Asian subjects (29) and one including subjects with European ancestry (30). As far as data in the Asian population is concerned, CD80 and ALOX5AP SNPs have been associated with SLE susceptibility and genetic interactions between BLK and DDX6 and between TNFSF4 and PXK have been observed (29). Conversely, in European subjects a new locus associated with SLE has been discovered on chromosome 12 falling within an intergenic region, located upstream of PRICKLE1 and interleukin-1 receptor-associated kinase 4 (IRAK4).

With regard to epigenetic changes, DNA methylation has been implicated in the pathogenesis of SLE, while little is known about hydroxymethylation in this process. 5-hydroxymethylcytosine (5-hmC), a newly discovered modified form of cytosine suspected to be an important epigenetic modification in embryonic development, cell differentiation and cancer. Zhao *et al*. provided evidence that 131 genes, including immune-related genes such as SOCS1, NR2F6 and IL15RA, that are up-regulated in SLE $CD4^+$ cells display increased 5-hmC in promoter regions compared with healthy controls (31).

In the field of innate immunity, the development of neutrophil extracellular traps (NETs) has been identified as an important pathogenic mechanism in several autoimmune diseases including SLE. In this regard, Lood *et al*. demonstrated that mitochondrial DNA, namely elevated mitochondrial radical oxygen species synthesis is a leading actor in the scenario of NETosis being able to drive this phenomenon in neutrophils isolated from SLE patients (32). Of interest, NETosis in SLE can also be enhanced by circulating apoptotic microparticles (33). Neutrophils are also capable to produce IL-6 upon stimulation with toll-like receptor (TLR) 8 agonists and IFNα has been recently identified as a powerful stimulus to enhance this process in SLE (34). Abnormalities of DCs isolated from patients with SLE have also been reported being the expression and function of the inhibitory receptor immunoglobulin-like transcript 4 hampered in this disease (35).

Several studies reported about phenotypic and functional features of circulating B and T lymphocytes as well as the serum concentration of cytokines, chemokines and other soluble mediators in SLE. With regard to pathogenic T helper (h) 17 cells, recent data demonstrated a link between these cells and gut microbiota. In fact, SLE but not healthy control fecal microbiota is able to induce the differentiation of $CD4^+$ naïve T lymphocytes into Th17 cells thereby hampering the Treg/Th17 cell ratio (36). Th17 cells can also be induced upon binding of ICs to FcγRIIIa on $CD4^+$ T-cells through Syk phosphorylation (37). Follicular T helper (Tfh) cells have a crucial role in regulating immune responses within secondary lymphoid follicles by directing B cell differentiation towards memory B cells and plasma cells. Tfh cells are expanded in patients with SLE, mainly those with more active disease, and are directly correlated to parameters related to B-cell hyperactivity such as including serum IgG, ICs and autoantibodies (38). With regard to $CD8^+$ T cells, the demonstration of signalling lymphocytic activation molecule family member 4 (SLAMF4) has been linked to reduced cytotoxic activity and may explain at least in part the reduced response to infections in SLE patients (39). Among recently identified T lymphocyte subpopulations, DN T cells can be induced by IL-6 and IL-23, are expanded in SLE and are associated with disease activity (40). Angiogenic T cells (Tang), a specific T cell subset involved in the repair of damaged endothelium, are expanded in SLE, mainly in those displaying anti-dsDNA antibodies (41). In addition, these cells display features of immune-senescence, namely they lack CD28 on the cell surface (42). Of interest, the total proportion of circulating $CD28^-$ cells is strongly associated with disease activity and in particular with LN (43).

With regard to B lymphocytes, pronounced Syk and Btk phosphorylation was observed in these cells from patients with active SLE compared to those of healthy individuals. Syk and Btk do not only transduce activation signal through B cell receptor (BCR), but also mediate crosstalk between BCR and TLRs and the JAK-STAT pathway (44). The glucocorticoid-induced leucine zipper (GILZ) protein, an endogenous mediator of anti-inflammatory effects of glu-

Table I. Data from studies assessing genetic associations in SLE (genome wide studies are not reported)

Gene	Results	Study cohort	References
HLA and related genes			
CFB	rs1270942 associated to the ↑SLE susceptibility	Caucasian	10
DRB3, DRB4, DRB5	Not associated to SLE susceptibility	Korean	9
MICB	Allele G of rs3828903 associated to the ↑SLE susceptibility	Chinese Han	11
MSH5	rs3131379 associated to the ↑SLE susceptibility	Caucasian	10
Non-HLA genes			
CCR5	Genotypes CCR5/CCR5, CCR5/CCR5Δ32, and CCR5Δ32/CCR5Δ32 associated with SLE	Southern Brazilian	19
Fcγ receptor			
IIa	FCGR2A-131RR ↑SLE susceptibility,	Caucasian	20
IIb	2B.4 haplotype of FCGR2B ↑SLE susceptibility	Caucasian	20
IIIb	FCGR3B*01/*01 and FCGR3B*01/*02 genotypes associated with SLE	Southeast Brazilian	21
Ficolin	FCN2 rs17514136 SNP associated with ↑ SLICC T/T genotype for FCN2 rs3124954 SNP associated with LN	Southeast Brazilian	26
IL-6	-174G/C allele associated with SLE	Egyptian	12
IL-10	-1082 G/G and AA alleles associated with SLE	Egyptian	12
IL-12B	Haplotype rs17860508↑ risk for SLE Haplotype rs3212227 associated with the PLT count, urea and C3 level	Polish	13
IL-17A	Not associated to SLE susceptibility	Egyptian	14
IL-17F	The AA genotype of rs763780 more frequent in females with SLE The AA genotype of IL-17F rs2397084 associated with anti-dsDNA+	Egyptian	14
IL-19	rs2243188 SNP associated with LN	Chinese Han	18
IL-27	Haplotype rs181206C/rs153109G ↑ risk for SLE Haplotype rs181206T/rs153109G ↓risk for SLE	Polish	13
IL-31	rs7977932 C/G polymorphism associated with SLE	Chinese	15
IL-32	rs28372698 SNP associated with the ↑SLE susceptibility	Chinese Han	16
IL-33	Lower expression of allele G for rs1929992 in SLE	Chinese Han	17
MX1	-88G/T SNP and CTA haplotype (-123 C, -88 T, -20 A) associated with ↑SLE susceptibility	Kuwaiti with Arab ancestry	22
PLA2R1	rs4664308 and rs3792192 associated with SLE rs4664308 associate with LN	Chinese Han	23
PTPN22	Haplotypes rs1217414 and rs3811021 ↓risk for SLE Haplotype rs3765598 ↑ risk for SLE	Chinese Han	28
TLR-9	rs352139 (G + 1174A) SNP ↑SLE susceptibility	Egyptian	24
TNFAIP3	13 SNPs associated with SLE	Chinese Han	25
Vitamin D receptor	BsmI polymorphism (BB genotype) associated to LN	Egyptian	27

5-HTTLPR: serotonin transporter gene; CCR5:chemokine receptor 5; HLA: Human leukocyte antigen; IL: interleukin; LTα: intronic lymphotoxin-α; TLR: Toll-like receptors; TNF-α: tumour necrosis factor; TNFAIP3: tumour necrosis factor alpha-induced protein 3

cocorticoids (GC), is downregulated in SLE naïve B cells (45) and so it is the complement receptor type 1, however for the latter its inhibitory capacity is not impaired (46). Finally, regulatory B (Breg) cells are decreased in patients with LN (47).

Biomarkers

Urinary biomarkers

Early diagnosis, correct assessment of disease activity and monitoring of disease flares in patients with LN remain great challenges due to the lack of valid biomarkers with good sensitivity and specificity profiles. In recent years, several promising, non-invasive candidate biomarkers have been evaluated, but their utility in routine clinical practice has yet to be determined.

Urinary biomarkers are attractive candidates since relatively easy to measure and reflecting the local pathophysiological changes.

Urinary B cell activating factor (uBAFF) and proliferation-inducing ligand (uAPRIL) (that help activation, maintenance and plasma cell survival) and urinary osteoprotegerin (uOPG) (produced by the kidneys and lymphoid cells) levels are raised significantly in patients with proliferative lupus nephritis with respect to healthy controls and patients with active lupus without nephritis. Their levels seem to reduce after treatment, especially in responders; uOPG has a potential to predict poor response to therapy and relapse of LN (48).

Other urinary markers are emerging as an indicator of disease activity. Among them, urinary podocyte excretion assessment, performed by immunofluorescence, seems to be particularly higher in patients with class IV LN (49); urine progranulin (uPGRN) levels (a multipotent growth factor), particularly in combination even with high serum levels, appear to have a good performance in discriminating active LN patients (50); urinary pentraxin 3 (uPTX3) (which is known to be involved in the regulation of the innate immunity system) levels were significantly higher in active LN patients compared with patients in remission or healthy controls and are associated with indices of tubulointerstitial lesions, being a possible biomarker of disease progression (51).

The serum TNF-like weak inducer of apoptosis (TWEAK) levels had proved to be a crucial determinant for a high SLEDAI score and renal involvement in patients with SLE (52), even if in another recent study, they seem not to correlate to other disease manifestations, such as CNS involvement (53). Serum insulin-like growth factor binding protein-2 (IGFBP-2) is a promising biomarker for LN, both for clinical activity and histopathological damage indexes (54).

Autoantibodies

Many recent papers have evaluated the association of subgroups of autoantibodies with specific clinical features of SLE, aiming at a better understanding of its pathogenesis and their prognostic value.

In a retrospective study on LN patients with a median follow-up period of 16.8±9.4 months, Wang *et al*. found that the prevalence of p-ANCA is not rare (26 of 154 patients), that more multisystem damage occurred in ANCA positive than in ANCA negative LN patients. However ANCA positive LN patients showed high scores on the pathological chronic index, outlining ANCA as an independent risk factor for poor renal outcomes in LN patients (55). Two prospective studies have evaluated the role of autoantibodies reactive to classic complement activation proteins and regulators of early complement activation. In the first, the combination of positive anti-C1q antibodies and low level of C3 showed the highest reasonable predictive values for LN flare (56). Conversely, in the second, comparing anti-C1q with anti-C3b IgG antibodies, these last seem to be more specific for LN (57).

Considering the difficulty in differential diagnosis, the detection of new biomarkers for NPSLE could be very useful in clinical practice. Starting from previous reports on increasing serum levels of anti-microtubule-related protein 2 (MAP-2) antibodies in NPSLE patients, a recent study confirmed that these autoantibodies are highly specific for NPSLE, being also elevated in the cerebrospinal fluid (58).

Other serological markers

Bonciani *et al*. demonstrated that homocysteine serum levels are higher in patients with SLE than healthy controls and appear to correlate with active skin manifestations both in patients with SLE and cutaneous lupus erythematosus (CLE) (59). A close relationship between the serum level of prolactin and SLE disease activity, as well as the titres of the ds-DNA antibody, IgM and IgG has been suggested (60). The frequency of programmed death ligand 1 (PD-L1)-expressing neutrophils was significantly elevated in SLE patients, especially in subjects with high SLEDAI score, and decrease during treatment: it has been hypothesised that the increased PD-L1-expressing neutrophils may act as a negative feedback mechanism in response to excessive autoimmune response during disease activity in SLE patient (61). Zhao M *et al*. evaluated the discriminatory power of gene methylation for SLE patient. As result, significant hypomethylation of two CpG sites within IFI44L promoter has been demonstrated in patients with SLE compared with healthy controls and patients with other autoimmune rheumatic disease, as well as in SLE patients with renal damage (62).

Clinical manifestations

The disease has a wide spectrum of well-known clinical manifestations. It has recently been highlighted that age of onset influences clinical and laboratory profile. Male gender is associated with a higher level of disease activity at the time of diagnosis independently of age or race/ethnicity and time to criteria accrual, but the clinical phenotype in the disease course does not seem to be strikingly different in both genders (63). A retrospective cohort study underlined that SLE patients display a higher death rate compared to the general population, and such rate is higher in man than in women. While the most common cause of death, in patients aged 20–39 years, was musculoskeletal and lupus-related causes on the contrary in those aged over 40 years the most common causes of death were malignancy and cardiovascular disease (64).

Neuropsychiatric involvement

Subtle NPSLE syndromes like emotional disorders including depression and anxiety are often considered as "non-NPSLE" when the patients have no history of "neuropsychiatric disorders" and normal conventional brain MRI scans. Bai *et al*. found that depression and anxiety were really common in "non-NPSLE," and they were strong risk factors of each other. Depression was associated with disease activity, anxiety with negative anti-P0 antibody, while both were associated with proteinuria and higher cumulative dosage of HCQ (65). These symptoms showed higher prevalence in SLE females compared to SLE males and control females, with a negative effect on the quality of life in both genders. In the female patients a correlation between depressive/anxiety symptoms and unemployment, as well as the use of higher doses of corticosteroids was observed (66). Age, disease activity, anxiety and depression were significant determinants of sleep quality, impairing the health-related (HR) QoL. In particular, anxiety was related to some of the sleep quality components, including sleep latency, sleep disturbance and overall sleep quality, while depression was related to sleep efficiency, need for sleep medications and daytime dysfunction (67). Patients with insomnia symptoms showed increased perceived stress, less

effective coping strategies, and higher rates of psychiatric symptoms, especially depression, compared to SLE patients with no insomnia symptoms. Furthermore these patients showed more frequently a renal involvement reflecting a greater degree of disease severity in SLE patients (68). SLE patients with headaches, especially those with migraine, were found to have less cerebral grey matter (GM) and larger white matter (WM) volumes compared to SLE patients without headaches. However, headaches were not associated with the presence of neuronal anti-NR2 and anti-P antibodies (69). Among major NPSLE symptoms, epilepsy, which resembles autoimmune encephalopathy (AE) features, is most likely attributed to more complex mechanisms than to the action of a single antibody against neuronal cell membrane antigens. This conclusion is supported by the different neuro-imaging and laboratory findings in SLE patients with epilepsy compared to those without (70). Other psychiatric features such as executive dysfunction, attention deficit and hyperactive disorder (ADHD), obsessive-compulsive disorder (OCS), and movement disorders are common in SLE and could be the manifestation of autoimmune mediated basal ganglia dysfunction (71). As the diagnosis of NPSLE is sometimes difficult and SLE patients can present with isolated psychiatric symptoms, clinicians should keep in mind that SLE can present with pure psychiatric symptoms and mimic mental illness, especially during atypical presentation or refractory mental illness. Is it therefore relevant to screen for NPSLE young women hospitalised in psychiatric department (72). Post-steroid neuropsychiatric (PSNP) disease is a specific clinical feature of NPSLE treated successfully with immunosuppressive therapy in the majority of cases (73). Previously published attribution models for NPSLE can be useful in diagnosis in routine clinical practice and their performance is superior in major neuropsychiatric manifestations. The Italian Study Group model is accurate, with values ≥7 showing the best combination of sensitivity and specificity (74).

Renal involvement

LN is known to be one of the most serious complications of SLE and it is the major predictor of poor prognosis. The presence of autoantibodies directed against several cytoplasmic (ANCA) plays a very important role in the pathogenesis of LN. Multisystem damage and higher frequency of antinucleosome antibodies, antihistone antibodies, antimitochondrial M2 antibodies, and anticardiolipin antibodies occurred in ANCA-positive LN patients compared to ANCA-negative. Moreover, ANCA-positive LN patients showed high scores on the pathological chronic renal index and had poor renal outcomes (75). In an international multi-ethnic/racial observational cohort of newly diagnosed SLE patients, LN occurred in 38.3% of subjects, often as the initial presentation with a poor prognosis in terms of end-stage renal disease (ESRD) (76).

SLE ESRD patients with anti-phospholipid antibodies (aPL)/lupus anticoagulant (LA) had higher all-cause mortality risk than SLE ESRD patients without these antibodies, while the effects of aPL/LA on mortality were comparable among non-SLE ESRD patients (77).

Tubulointerstitial (TIN) features are often under-recognised in SLE. Renal biopsies from 142 patients who underwent repeat biopsy (RB) were evaluated for: inflammatory interstitial infiltrates; interstitial fibrosis; tubulitis; and tubular atrophy. The study confirmed the presence of at least one TIN lesion in up to 60% of patients at first biopsy and 75% at RB. Tubular atrophy that was found to be strongly associated with interstitial fibrosis showed the highest rate of worsening between the reference and the second biopsy patients. The opposite transition from moderate-severe to absent-mild findings was frequent, especially for tubulitis (and inflammatory infiltrates), regressing in around 70% of the cases (78).

Gastrointestinal involvement

Intestinal pseudo obstruction (IPO), originally considered to be an uncommon complication of SLE, may occur as initial presentation of SLE, thus leading to difficult diagnosis and delayed treatment. It always occurs concomitantly with pyeloureterectasis or megacholedochus due to vasculitis of the visceral smooth muscles, which implies poor prognosis. Furthermore the incidence of IPO is related to the activity of SLE disease (79).

Pulmonary involvement

Pérez-Peñate *et al*. carried out a prospective study using an algorithm based on pulmonary arterial hypertension (PAH) predictors such as dyspnea, DLCO, and N-terminal pro–brain natriuretic peptide (NT-proBNP). The study confirmed these last predictor factors of pulmonary hypertension (PH) and PAH and SLE-PAH low prevalence (80). Pericardial effusion and positive anti-RNP antibody have been identified as risk factors for PAH in SLE, however long SLE disease duration, the presence of interstitial lung disease, without acute skin rash, positive anti-SSA antibody, low SLEDAI and ESR, and high uric acid levels were also associated (80).

Haemodynamic variables are of greater importance in determining HRQoL of SLE-PAH patients with SLE disease activity. In particular cardiac output was found to be the strongest independent predictor for both physical and mental component summary (PCS-MCS), while SLE disease activity was also independently associated with PCS scores (81).

Nail and nailfold involvement

There is a large variety of nail abnormalities in SLE patients and also a great variety of nailfold videocapillaroscopy (NVC) abnormalities, similar to early scleroderma pattern. Higuera *et al*. found NVC abnormalities in 43,8% of the nail distrophy (ND) patients and in 13.8% of the patients without ND. They observed an association between ND with an increase damage index and with NVC abnormalities (82).

Haematological manifestations

The severity of thrombocytopenia can be a useful independent prognostic factor to predict survival as also the response to treatment (83).

Comorbidities

In the last decades the survival of patients with SLE has improved, due both to prompt early diagnosis and to more effective treatment strategies of the disease and of its comorbidities. SLE complications and comorbidities can be caused both by disease activity and by the adverse events of immunosuppressant drugs.

Infections represent the most common associated comorbidity in SLE patients, and seem to be the leading cause of morbidity and mortality in this disease. Many infections have a higher prevalence in SLE than in healthy subjects. An analytic retrospective study that evaluated the incidence of infections in 144 SLE patients and their association with therapies with a 5 year follow up reported a high incidence of urinary tract infections followed by upper airway infections, pneumonia, *Herpes zoster* (HZ) candidiasis and tuberculosis. Steroid and cyclophosphamide (CYC) treatment were associated with urinary infection; while steroids, mycophenolate mofetil (MMF) and cyclosporine correlated to airway infections (84). In SLE central nervous system (CNS) may be susceptible to infections. The prevalence of cryptococcal meningitis (CM) in SLE patients is about 0.5%. A recent retrospective study including 108 women investigated the independent gender-specific contributing risk factors for CM. Results indicated that the use of immunosuppressant agents, steroids and rheumatic diseases were common in CM female patients. However, SLE or other systemic immune diseases were independent risk factors to develop this infection, highlighting the importance to monitor patients with SLE receiving immunosuppressive agents at risk to develop CM infection (85). When focusing on the causes of hospitalisation for infection complications in SLE patients, number of hospitalisation for HZ was increased compared to the general population from 2000 to 2011. On the other hand, a decreasing trend was found in the hospitalisations due to *Pneumocystis pneumonia*. The evaluation of all causes of hospital admissions in more than 1600 patients with SLE revealed that, excluding the hospitalisations for SLE as primary diagnosis, the major causes were represented by cardiovascular manifestations and pregnancy complications. The hospitalisation for malignancies was higher compared to the general population (86). In this regard, several studies reported a major risk to develop malignancies in patients with chronic inflammatory and autoimmunity diseases. Recently, a nationwide study in patients with systemic autoimmune rheumatic diseases revealed that in SLE patients, the cancer incidence rate (per 100.000 person-years) was of 316.4 with an increased prevalence of lung and thyroid cancer (87). With regard to the osteonecrosis of the femoral head (ONFH), a recent study in Korean SLE patients associated three SNPs of complement receptor type 2 with this manifestation (88).

Finally, it is important to remark that a recent study on more than five thousand SLE patients reported a significant association between SLE and inflammatory bowel diseases, in particular Crohn's disease. This data indicates the importance to investigate gastrointestinal manifestations in SLE patients in order to early recognise this possible association (89).

Cardiovascular risk

Patients with SLE have a considerable risk for cardiovascular morbidity and mortality due to coronary heart disease and accelerated atherosclerosis. The prevalence of coronary microvascular dysfunction (CMD) assessed by transthoracic Doppler-derived echocardiography for coronary flow velocity reserve measurement in the left anterior descending coronary artery was much higher in SLE patients compared to controls (67% and 26%, respectively) (90).

Valvular heart diseases are also common in SLE patients. Performing a transthoracic echocardiogram in 211 SLE patients, Vivero *et al*. found a one-in-four prevalence of significant valvulopaty. Valvular thickening prevalence was higher in anti-Sm antibodies positive patients, while hypertension and double positivity aCL/LA were found as predictors of valvular disfunction. Age, longer disease duration, thrombocytopenia, lymphopenia and aPL positivity were strongly associated with both forms of valvulopathy (91). A retrospective case-control analysis of 5018 patients with SLE and 25090 controls frequency-matched on age and sex showed a proportion of aortic aneurysm increased by an OR of 4.5 among patients with SLE compared with the controls (92). To assess premature atherosclerosis CIMD (Carotid intima-media thickness) and FMD (flow-mediated dilatation of the brachial artery) were performed in 100 SLE patients, 50 of whom had nephritis. CIMD values did not significantly differ in patients with LN compared to SLE without nephritis whereas FMD was significantly lower in LN patients (93).

Arterial stiffness, one of several underlying mechanisms of accelerated atherosclerosis, can be assessed by metrics of pulse wave velocity (PWV).

In SLE patients with normal renal function and without renal damage, and with no history of coronary heart disease or peripheral arterial disease, those with increased PWV were more likely to have organ damage measured using the SLICC/ACR Damage Index (SDI ≥1) than those with normal PWV (94).

The incidence of thrombosis in patients with SLE is 25 to 50-fold higher than in the general population. In 219 patients with recent-onset SLE, 16% developed thrombotic events (27 venous, 8 arterial). Risk factors for venous thrombotic events included cutaneous vasculitis, nephrotic syndrome, taking prednisone, and LA in combination with anti-RNP/Sm antibodies. Patients with arterial thrombotic events were older, smokers, and had hypertension, diabetes mellitus, dyslipidaemia, at least 2 traditional risk factors, nephrotic syndrome, chronic damage, and a higher cumulative dose of prednisone (95). It is well known that chronic glucocorticoid (GC) therapy is a primary factor that influences the cardiovascular risk in SLE patients. A more than 7 year monitoring in 101 SLE patients found a directly proportional relationship between the increase in Framingham Cardiovascular Risk Scale and the cumulative steroid dose (96).

Treatment

Phase III and post-marketing trials (real-life registers)

In 2016, data emerged on the use of new drugs in SLE and a new knowledge on traditional drugs has been achieved; for the latter, international initiatives and registries gave a substantial contribution, especially in newly diagnosed patients (97-98).

As far as biological drugs are concerned, some interesting data were published on belimumab confirming their effectiveness on several clinical outcomes. In a *post-hoc* analysis on 966 patients on GC at study entry in two randomised clinical trials of belimumab in SLE, a significantly smaller increase in cumulative corticosteroid dose over 1 year and a significant decreases in oral GC dose, in the belimumab group compared with the placebo group were found, thus suggesting a GC-sparing effect of the drug (99).

Pooled data from two open-label studies that enrolled patients who completed BLISS-52 or BLISS-76 showed a low incidence of organ damage accrual as 85.1% of patients had no change from baseline in SDI score after 5 years of follow-up (100). This observation was also confirmed in a real life setting by Iaccarino *et al*. in a prospective cohort of 67 SLE patients from two Italian centres: by comparing disease flares occurrence before and after belimumab initiation, they found that flare rate was lower 1 and 2 years after starting belimumab and no further damage accrual was observed (101).

Since the belimumab launch, other data from real life are accumulating. The OBSErve registry in Germany retrospectively collected data on 102 patients treated with belimumab as an add-on therapy in active SLE; during the first 6 months of treatment, a reduction SLEDAI scores and glucocorticoid usage was registered and 78% of patients showed an improvement in overall disease activity of at least 20% in their physician's judgment (102). Similarly, a clinical effectiveness and a steroid-sparing effect of belimumab in clinical practice was also reported by Schwarting and coworkers on 48 Brazilian patients (103).

In 2016, new data from real life were also published for Rituximab from the international Registry for Biologics in SLE; the estimated off-label use of Rituximab resulted limited to 0.5–1.5% of SLE patients and refractory renal, musculoskeletal and haematological manifestations were the main indications (104).

In 2016, new drug development failures were also registered. In the phase III trial on 1164 SLE patients with moderate-to severe disease activity (ILLUMINATE-1), subcutaneous injections of tabalumab (a monoclonal antibody that neutralises membrane and soluble B-cell activating factor) failed to demonstrate clinical superiority over placebo despite the demonstration of biological activity in inducing changes in anti-dsDNA, complement, B cells and immunoglobulins levels (105). In the other phase III trial (ILLUMINATE-2) the primary end-point was achieved by the dosage of 120 mg every 2 weeks but key secondary end-points were not met (106). Similarly, no benefit was observed in serum creatinine concentration, glomerular filtration rate, urine protein/creatinine ratio or renal flare rates (107). Because of mixed phase III trials results, further development of this drug was stopped. Safety, tolerability, efficacy and pharmacodynamics of the selective JAK1 inhibitor GSK2586184 was evaluated in patients with active SLE; however, from the interim analysis no significant effect on surrogate endpoints was found and significant safety data were identified thus leading to immediate dosing cessation (108). As far as non-biological immunosuppressive drugs are concerned, new data emerged for lupus nephritis. The 10-year follow-up of the MAINTAIN Nephritis Trial comparing azathioprine (AZA) and MMF as maintenance therapy of proliferative lupus nephritis was published; these data confirmed that in Caucasian patients MMF is not superior to AZA as maintenance therapy (109).

Moreover, in an open randomised controlled parallel group study in 150 patients with active lupus nephritis, Mok *et al*. showed that tacrolimus is non-inferior to MMF for induction therapy (1110.

Novel target therapies: phase I and II trials

Thanks to a better understanding in SLE pathogenesis, today new immune-modulating drugs are currently administrated in patients resistant to conventional treatments. In relation to a IFNα blockade by sifalimumab, a new analysis about safety, efficacy and pharamacokinetics (PK) properties has been conducted in 298 SLE patients (111). Confirming phase Ib study PK data, it has been demonstrated that fixed dosing regimen *versus* body-weight adjusted dosing, despite clinical factors (body weight, signature gene, steroid use, dose) do not explain inter-subject variability in PK parameters. Consistent with previous and currently results, fixed doses of sifalimumab could be evaluated as a new therapeutic strategy. Efficacy and safety of rontalizumab, an anti-IFNα monoclonal antibody, have been also investigated in a large phase II trial (112). In this study, 238 patients with active SLE were randomised to rontalizumab (159 patients) or placebo. Primary end point was efficacy assessed by the reduction in disease activity established by BILAG and SRI. Efficacy was also investigated by an exploratory measure of IFN regulated gene expression (IFN signature metric-ISM). Interestingly the primary and secondary end points were not met in the whole population and in patients with high-ISM score. In these 2 groups, efficacy response rates assessed were similar between the rontalizumab and placebo groups. However, the experimental drug was associated with improvement in disease activity, reduced flares and decreased steroid use in the subgroup patients with SLE low-ISM score as shown by the exploratory subgroup analysis.

Recently a new confirmation related to safety, efficacy and improvement in SLE patients treated with epratuzumab was provided by a Japanese trial (113). Study results demonstrated a moderate reduction in total B cells ($CD19^+CD22^+$), a linear PK profile, common adverse events as well as an amelioration of moderate-severe SLE activity. Concerning long-term safety, treatment with epratuzumab was well tolerated for up to 3.2 years and associated with relevant improve-

ments in disease activity and (HR) QoL, while steroids were reduced (114). After epratuzumab, a new anti-CD22 monoclonal antibody, namely SM03, was administrated for the first time in Chinese SLE patients. Unlike epatuzumab, SM03 is a recombinant human/mouse chimeric IgG1 monoclonal antibody. In an open, multicentre, parallel group, multiple-ascending-dose, phase I study the authors evaluated PK profile in addition to the efficacy and safety on 29 SLE patients (115). They found a clinical improvement in a mild-severe disease-activity, a decreased in $CD19^+$ B cell count, without serious adverse events (the commonest adverse events observed were infections and infestations as reported with other biologic drugs).

New insights from preclinical studies

Focusing on LN, the major cause of morbidity and mortality of SLE disease, a novel study have attributed to bortezomib suppressive action on the renin-angiotensin system (RAS). Bortezomib as proteasome inhibitor is able to prevent glomerulosclerosis independently of immunosuppressive capacity. In fact, within the glomeruli of New Zealand Black and White (NZB/WF1) mice, bortezomib suppresses angiotensin (AT) II and AT1R expression, thereby blocking type I collagen synthesis (trough TGF-β down-regulation) underling renal fibrosis (116). Besides to affirmed immune effector cells depletion, bortezomib promises new approach for the treatment of refractory SLE at risk to develop glomerulosclerosis. Considering the growing interest in the IFN activity on SLE pathogenesis, as demonstrated by current clinical trials, an IFN-dependent pristane-induced mouse model of SLE has remarked the role of Bruton's tyrosine Kinase (Btk) in autoimmune disorders. A new Btk inhibitor, namely M7583, administrated in different experimental lupus models sharing TLR7 expression but representing different subclinical and pathogenic patterns of disease, is able to suppress clinical manifestation without however, modifying IFN-gene expression (117).

In the last years, the role of mesenchymal stem cells (MSCs) is gaining growing interest in the therapeutic approaches of the SLE treatment. Recently, in a NZB/W mice model, it was discovered a novel mechanism in MSC able to ameliorate clinical SLE manifestations (118). In this respect, the infusion of human bone marrow-derived MSCs was able to ameliorate glomerulonephritis, proteinuria, sialadenitis, and survival along with a decrease of autoantibodies. Interestingly, a modulation of Tfh cells, B cell and plasma cells in the germinal centres has been claimed as the underlying mechanism.

To overcome the morbidity and mortality due to the major immunosuppress drugs for LN treating, researchers are trying to replace CYC with chemokine-blocker (119). In particular Devarapu *et al*. have shown that the combined blockade of CCL2 and CXCL12 (chemokine monocyte chemoattractant protein-1 and homeostatic chemokine stromal cell-derived factor-1), in MRL/lpr model mice, obtained the same results in term of proteinuria, glomerulonephritis, renal injury, as well as high dose of CYC.

Pointing out the key role of B cell in the pathogenesis of SLE, biological treatment aimed at depleting B cells are under intense investigation. In this contest the use of humanised anti-human CD19 monoclonal antibody (MEDI-551) is becoming a potential novel treatment in SLE disease thanks to its broad spectrum on B cells differentiation stages as well as on autoantibody-secreting plasma cells. After the administration of single or repeated doses of MEDI-551 on Sle1.hCD19-Tg mice, a robust B cell depletion in the spleen was observed, along with an effective reduction of autoantibodies and inflammatory cytokines in the sera (120).

Recently, the action of benzediamine in the MRL/lpr mice was also investigated. Considering that FC-99 (benzediamine derivate N1-[(4-methoxy)-methyl]-4-methyl-1,2-benzenediamine) interacts with IRAK4, and the expression of BAFF derives from IRAK4/TLR4/NFkB signalling activation, a reduction of Ig in the animal sera as well as a reduction of B cell in the spleen was observed (121). In addition, an inhibition of DC activation in the spleen as well as a reduction of BAFF levels in the sera, spleen and kidney were observed. All these events led to the attenuation of LN blocking IC deposition, lymphoid cell infiltration pro-inflammatory cytokine expression.

Although GC represent a highly effective treatment in SLE and overall in life-threating manifestation, severe side effects may limit their use. To overcome this problem, liposome-based methylprednisolone hemisuccinate nanoparticles have been tested as alternative route of corticosteroid administration. Comparing the steroidal nano-drug formulation with similar doses of free GC, an effective superiority on clinical manifestations (lymphoid tissue, renal damage), on the suppression of anti-dsDNA antibodies levels and on the animal survival were observed (122). Considering the structure, the steroid nano-drug is able to penetrate in the inflamed tissues reducing steroid accumulation in other healthy sites, and favours a slow release in inflamed tissues.

Conclusion

To provide a cutting edge on the most relevant findings regarding SLE pathogenesis, clinical, laboratory as well as comorbidities and novel treatments, we have summarised the principal data emerged during the last year. However a major knowledge in the SLE pathogenesis and consequently the implication of therapeutic strategies are still needed to better prevent and cure SLE.

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