Review

One year in review 2016: systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a highly variable course and prognosis. The management of the disease is still a clinical challenge for the treating physicians as many aspects regarding the disease pathogenesis, clinical picture and outcomes remain to be elucidated. New and interesting data are emerging; here the recent literature on SLE pathogenesis, clinical and laboratory aspects, as well as treatments and comorbidities, are reviewed and the main findings summarised in order to provide a bird's eye on the relevant papers on these topics.

Introduction

The aim of this review is to provide an overview of the new data that has emerged on disease pathogenesis, clinical and laboratory findings, treatment and comorbidities. We performed a MEDLINE search of English language articles published from the 1st January to 31st December 2015 using MESH terms and free text words for the following search keys: systemic lupus erythematosus, aetiology, pathogenesis, biomarkers, autoantibodies, genetic markers, diagnosis, symptoms, signs, manifestations, comorbidity, complications, therapy, therapeutics, treatment, pharmaceutical preparations, drugs. The most relevant articles were selected for inclusion in this review.

Pathogenesis

Genetic and environmental factors

A large study conducted on 1467 patients with SLE and 2377 controls mapping the 3p14.3 locus confirmed the genetic association of the 3p14.3 locus with SLE in Europeans and points to ABHD6 as the major susceptibility gene in the region. As a consequence, up-regulation of ABHD6 may have a pathogenetic role in the development of SLE in European patients (1).

Occupational exposure to crystalline silica (cSiO2) has been aetiologically linked to increased incidence of SLE. In an animal model, Bates *et al*. demonstrated that cSiO2 exposure modulates both latency and severity of autoimmunity in the lupus-prone mouse, reducing latency and increasing intensity of glomerulonephritis. cSiO2-induced pulmonary inflammation and ectopic lymphoid neogenesis, so lungs became a platform triggering systemic autoimmunity and glomerulonephritis (2).

Marked sexual disparity is well known in SLE, suggesting a relationship between sex hormones and disease pathogenesis. Interestingly, oestrogen administration (17-β-estradiol) in a lupus prone mice model showed increased levels of BLyS as well as of anti-C1q and anti-dsDNA antibodies, leading disease progression (3).

Moreover, Yang *et al*. speculated that inflammasomes in male and female SLE macrophages are differentially activated, demonstrating that Nucleotide Oligomerisation Domain (NOD)-like Receptor Containing Protein 3 (NLRP3) inflammasome is hyperactivated in both male and female, while Absent In Melanoma 2 (AIM2) inflammasome is increased in male SLE patients and decreased in female. Given these results, sex-linked different inflammasome expression may lead to different pathogenetic mechanisms and disease severity in male and female (4).

Apoptosis and neutrophil extracellular traps (NETs)

The disregulation of apoptosis is a key factor for the development of SLE. Li *et al*. demonstrated that defects on interferon-induced mechanosensing impede apoptotic cell clearance in SLE. Follicular translocation of marginal zone (MZ) B cells in the spleens of lupus mice disrupts marginal zone macrophages (MZMs), which normally

clear apoptotic cell (AC) debris and prevent follicular entry of apoptotic cell autoantigens (AC-Ags). Phagocytosis of ACs by splenic MZMs requires the megakaryoblastic leukaemia 1 (MKL1) transcriptional coactivator–mediated mechanosensing pathway. In this study the authors observed that type I interferon down-regulates MKL1 in MZMs and the loss of MKL1 expression in MZMs led to inability to clear ACs. Aggregation of plasmacytoid DCs in the splenic perifollicular region, follicular translocation of MZ B cells, and loss of MKL1 and MZMs were observed in both a murine lupus model and in the spleens of patients with SLE (5).

A recent pre-clinical study suggested a role for the apoptotic microvescicles (MVs) in the increased activation of dendritic cells (DC). Indeed, apoptotic MVs in a lupus-prone mice contained modified chromatin compared to control mice, mediating an enhanced activation of DC directly correlated with production of IL-6. The authors concluded that alteration of MVs chromatine may change their immunogenicity and may result in breaking the tolerance in SLE (6).

Knight *et al*. demonstrated the pathogenetic role of the degradation and formation on neutrophil extracellular traps (NETs) in a pre-clinical model. Indeed, they showed that neutrophils from lupus mice have accelerated NET formation compared with controls, they form autoantibodies to NETs and have evidence of endothelial dysfunction. After treating mice with peptidylarginine deiminase (PAD) inhibitors (Cl-amidine and BB-Cl-amidine) a down-regulation of the expression of IFN-I regulated genes was observed as well as an improvement in endothelial function, a reduction of deposition of immune complex in kidneys, proteinuria and skin lesions (7).

Innate and acquired immunity

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate the expression of multiple genes by targeting mRNA. In T cells from SLE patients, miR-524-5p and miR-449b resulted over-expressed with a direct relationship with disease activity (8).

Another recent observation was that Let-7 miRNA is able to regulate tumour necrosis factor alpha-induced protein 3 (TNFAIP3) expression, an ubiquitin-editing enzyme that negatively regulates multiple NF-κB signalling pathways. Interestingly, Let-7 miRNA expression was significantly up-regulated in SLE patients with lupus nephritis (LN) suggesting a possible pathogenetic role in LN and a potential new therapeutic target (9).

Moreover, Rapanagudi *et al*. studied the functions of cathepsin S, a protease driving MHC class II-mediated T and B cell priming, germinal centre formation and B cell maturation towards plasma cells. They observed that inhibition of cathepsin S by a cathepsin S antagonist in lupus prone mice suppressed expansion and activation of CD4 T cells, CD4/CD8 double-negative T cells, follicular B cell maturation to plasma cells and Ig class switch. The clinical result was prevention of lupus nephritis progression even when given after disease onset (10).

Zhang *et al*. showed that the frequency of circulating Follicular helper T-like (Tfh-like) cells was significantly increased in SLE patients compared to healthy controls and that they are capable of driving B cells to differentiate into IgG secreting plasma cells, acting like germinal centre follicular helper T cells(GC-Tfh). The frequency of Tfh-like cells correlated positively with the percentage of circulating plasmablasts, levels of serum anti-dsDNA antibodies and ANA (11).

Confirming these results Choi *et al*. in a case control study involving 48 SLE patients showed that Tfh-like T cells, were expanded in the blood of SLE patients compared to healthy controls. These cells produced IL-21 and have increased PD-1 expression, which correlated with disease activity, circulating plasmablasts and anti-dsDNA antibody positivity. According to these results, PD-1 expression in the future could represent a biomarker of disease activity and treatment response (12).

Biomarkers

Autoantibodies

In the last few years, new auto-antibodies have been associated with SLE but their clinical and prognostic significance is not fully elucidated; indeed, the main attempt of the latest studies is to understand their diagnostic and prognostic value in the clinical practice. In particular, for the early identification of the renal involvement, several studies attempted to identify new markers able to distinguish between inactive and active LN.

The diagnostic accuracy of anti-C1q to identify the patients with active SLE and/or active LN was tested in a case-control study by Chi *et al*. (13). As a result, anti-C1q were characterised by higher specificity with respect to anti-dsDNA or serum complement levels, while these two parameters displayed a better sensitivity.

Another study tested the correlation between the renal histology and several serological markers (anti-dsDNA, anti-C1q, anti-nucleosome, anti-ribosome P and C3/C4 serum levels) measured at the time of the renal biopsy and after 6-12 months (14). High titers of anti-C1q or anti-dsDNA were the main predictors to discriminate between proliferative and non-proliferative lupus nephritis.

In a case-control study, Li *et al*. tested the performance of anti-nucleosome antibodies as activity biomarkers in SLE (15). The authors observed that anti-nucleosome performed better than anti-dsDNA and serum C3 level in identifying active disease. Moreover, the fluctuations of the anti-nucleosome antibodies, anti-dsDNA and serum C3/c4 levels appeared poor predictors of subsequent changes in SLE activity.

Ishizaki *et al*. showed that in patients with silent LN the levels of C3/C4a and the complement haemolytic activity (CH50) appear significantly decreased while the tile of anti-SM and anti-RNP were significantly higher with respect to the patients with no renal involvement (16).

Hagberg *et al*. studied the role of antibodies directed against specific natural killer (NK) receptor in a SLE cohort (17); indeed, NK cells alterations can have an important role in SLE pathogenesis and the presence of specific antibodies against these cells could be an interesting finding. Indeed, the authors observed the presence of these autoan-

tibodies in a small number of patients but they demonstrated the ability of these antibodies to interfere with the NK activity.

Other serological and urinary markers

The relationship between interferon (IFN) and disease activity have been extensively studied. Kikuchi-Taura *et al*. assessed this association indirectly, through the CD64 expression on monocytes (mCD64), up-regolated by circulating Interferon alpha (IFN-α). They observed either a significant difference between mCD64 expression in SLE patients with respect to controls and a significant higher mCD64 level in patients with active SLE respect to the inactive ones (18).

In another study, the interferon I-inducible genes (LY6E, OAS1, OASL, MX1, and ISG15) expression was evaluated in SLE patients. All five genes were over- expressed in SLE compared to controls and their expression positively correlated with disease activity (19).

The identification of urinary markers is mainly addressed to find markers able to early identify LN patients or to screen SLE patients with a greater risk to develop renal impairment.

Gupta *et al*. evaluated the discriminatory power of the urinary prostaglandin D synthase (uPGDS) for LN (20). As result, the uPDGS levels group were significantly higher in active LN and a modest correlation was found between uPDGS and protein creatinine ratio but not with SLEDAI.

Clinical manifestations

The clinical spectrum of the disease is wide and highly variable among patients; in particular, significant differences in term of clinical manifestations and serological profile have been recently found in juvenile-onset SLE with respect to adult and late-onset SLE.

Moreover, damage accrual and loss of function are common expected outcomes in the natural history of the disease, nonetheless, age at disease onset >50 years was an independent risk factor for damage accrual and mortality (21). Doria *et al*. performed a two-year, retrospective, multicentre, study to evaluate the direct medical costs of care of SLE patients. They found that the medical cost of SLE in Italy is related to disease severity and flares occurrence. Medications identified as the main cost drivers, hypocomplementaemia and severe flares as the main cost predictors (22).

The most relevant clinical data by organ involvement are also provided below.

Neuropsychiatric involvement (NPSLE)

NPSLE comprehends a wide range of neurological and psychiatric syndromes, none of which are specific for SLE. Bortoluzzi *et al*. developed and validated a new algorithm based on a probability score to determine the relationship between NP events and SLE. The algorithm was constructed on a cohort of 228 SLE patients and it showed good performance in discriminating patients with NPSLE (23).

Lupus nephritis

Mavragani *et al*. developed a predictive model, based on clinical and laboratory parameters, aimed to estimate the risk of a severe subtype of LN. In detail, the presence of young age, musculoskeletal manifestations, new-onset hypertension, anti-dsDNA antibodies, increased number of leucocytes and cellular casts in urinalysis, increased serum creatinine and absence of nephrotic range proteinuria are highly associated of proliferative LN (class III/IV), while older age, malar rash, nephritic range proteinuria, normal C3, haematuria are highly associated with membranous class V lupus nephritis (24).

Hernandez-Molina *et al*. followed up 90 SLE patients after renal biopsy for LN and evaluated the presence of acute thrombotic microangiopathy (aTMA) and chronic vascular lesions (cTMA). Eleven patients (12.2%) had cTMA and 3 (3%) aTMA. At four years of follow-up, 28% of the cTMA group and 62% of the non-cTMA group were free of dialysis meanwhile aTMA was associated with dialysis (25).

Comorbidities

It is well known that SLE is associated with a large number of comorbidities including disease complications and treatment-related adverse events. Among these, cardiovascular complication are one of the major causes of morbidity and mortality in SLE.

Indeed, lupus patients have a risk of coronary artery disease that is 2–10 times higher than in the general population, with a greater increase in relative risk in younger patients group. Both traditional and non-traditional risk factors contribute to this higher prevalence (26). Peripheral arterial occlusive disease (PAOD) is one of the principal manifestations of atherosclerosis and it is a negative prognostic factor; its prevalence is higher in SLE patients than general population regardless other risk factors. PAOD risk is particularly elevated in female young SLE patients in the first year after SLE diagnosis (27).

Kiani *et al*. reported that women with SLE, in particular those between 45-54 years, have a higher prevalence of coronary artery calcium (CAC) than controls, even after adjusting for traditional cardiovascular risk factors; however, they did not observe strong evidence of an association between CAC and SLE disease activity and duration, low complement and anti-dsDNA (28).

Ruiz-Limon *et al*. investigated the potential mechanisms involved in the efficacy of fluvastatin in preventing atherothrombosis in SLE. Interestingly, they observed that one month of Fluvastatin treatment was able to reduce disease activity as well as lipid levels, oxidative status and vascular inflammation (29).

Interestingly, Ajeganova *et al*. demonstrated an inverse association between bone mineral density (BMD) and carotid intima media thickness. Risk factors for CVD (hypertension, smoking, dyslipidaemia, diabetes and oxidative stress) have been associated with increased risk of lower BMD (30).

Recently, the cancer risk associated with SLE has been reviewed in a meta-analysis suggesting that a close association between SLE and malignancy; Cao L *et al*. demonstrated an increased risk for non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), leukaemia and some non-haematologic malignancies such as laryngeal, lung, liver, vaginal and thyroid malignancies than in the general population.

The highest estimated risk occurs the first year from SLE diagnosis and after more than 20 years. The authors hypothesised that the chronic inflammation as well the autoimmune process may increase the lymphocyte proliferation rising the probability of a translocation of an oncogene, thus favouring the emergence of lymphoma. Interestingly, an increased risk for cervical cancer was not found in this study (31). On the other hand, Seyoung *et al*. reported an increased risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory disease (including SLE and rheumatoid arthritis) than in general population, independently of immunosuppressive drugs or steroid at baseline. These results suggest that SLE patients could be a target population for HPV vaccine (32).

Another frequent comorbidity in SLE patients is fibromyalgia (FM); data from the RELESSER-Transversal Spanish Registry, which includes SLE patients in a national multicentre retrospective charts review, confirmed that the prevalence of FM in Caucasian SLE patients is higher than in the general population, especially in later stages of disease. Depression, photosensitivity, oral ulcers and secondary Sjögren's were associated with FM developing in these patients (33).

In recent years, vitamin D deficiency has taken on great importance in systemic autoimmune disease including SLE; Dell'Ara *et al*. showed that vitamin D levels in Italian SLE patients are often suboptimal and disease flares during winter were associated with lower vit.D levels suggesting a close relationship between disease activity and VitD status (34).

Therapy

The number of effective treatments for SLE has been progressively growing. In fact, together to the traditional drugs, new therapies have been proposed to better deal against the SLE manifestations.

Traditional drugs

• *Antimalarial agents (AMs)*

The role of AMs in the treatment of SLE is well established and growing interest has emerged in the last few years toward these drugs. To confirm this trend, a registry-based cohort study in Denmark showed an increased and an earlier use of AMs after SLE diagnosis is made (35).

A retrospective study demonstrated that there is no relationship between ethnicity, sex or smoking and plasma Hydroxychloroquine HCQ concentrations and no drug interaction between HCQ and antiacids or inhibitors or inducers of CYP enzymes were found. The study also showed that a very low blood HCQ concentration is an objective marker of poor adherence to treatment in SLE. Retinal toxicity is confirmed a major complication of AMs with a dose and duration – dependent effect; the authors suggested <6.5 mg/kg as a safe dose (36).

Moreover, Chen *et al*. (37) in a a cohort study showed that HCQ use is protective toward diabetes mellitus development in SLE patients and the protective effect of HCQ is dose dependent: a cumulative HCQ dose ≥129 g (200 mg/day for 1.8 years) was associated with reduced risk of developing diabetes in SLE patients.

• *Traditional immunosuppressive drugs*

Mycophenolate mofetil (MMF) and cyclophosphamide (Cyc) are the drugs of choice for SLE and, in particular, renal involvement. A recent study by Fassbinder *et al*. compared the effects of these drugs on cellular and serological parameters in LN patients showing that MMF leads to a fast reduction of plasmablasts and plasma cells, whereas Cyc has no significant influence on these B cell subsets. Moreover, the free light chains are influenced significantly by MMF, not by CYC. These results suggest that both drugs lead to similar effects, but with different mechanisms (38).

Zabotti *et al*. (39) recognised that the assessment of mycophenolic acid (MPA) pharmacokinetics appears useful to optimise the maintenance therapy of lupus nephritis with MMF, possibly improving the efficacy and minimising the side effects with a target MPA AUC0-12h of 45–60 mg.h/l.

B-cell blockade

• *Rituximab*

Rituximab (RTX), a type I anti-CD20 monoclonal antibody (mAb), can induce incomplete B cell depletion in some patients with rheumatoid arthritis (RA) and SLE, thus contributing to a poor clinical response. In an *in vitro* study, Reddy *et al*. (40) found that type II mAb are more efficient than type I mAb at depleting B cells in sera from RA and SLE patients, they also demonstrated that internalisation of Rituximab influences the efficiency of depletion, and that Fcγ receptor type IIb (FcγRIIb) and the B cell receptor regulate this internalisation process. This suggested that internalisation of RTX is a probable "resistance mechanism" in patients with SLE. Therefore, slower-internalising type II mAb should be considered as alternative B cell-depleting agents for the treatment of RA and SLE.

From the clinical point of view, an Italian Multicentre Registry confirmed, the efficacy and safety of RTX in 134 SLE patients refractory to standard therapy. Interestingly, in case of retreatment, it has been observed a higher incidence of adverse events, especially infusion reactions and infections (41). In a large cohort of patients with juvenile SLE failing standard therapy, RTX was able to reduce disease activity biomarkers and GC cumulative dosage (42).

A retrospective study in 98 SLE patients showed that lymphopenia after RTX therapy is associated with a longer duration of depletion and better outcome (43).

Vital *et al*. (44) observed that the clinical response to rituximab in cutaneous manifestations of SLE depends on subtype. None of the chronic cutaneous lupus erythematosus (CCLE) patients responded, and new CCLE lesions were observed during B cell depletion, suggesting that initiation and activity of these lesions is not B cell dependent.

• *Belimumab*

Belimumab is a fully humanised monoclonal antibody that inhibits B-lymphocyte stimulator.

A prospective, multicentre observational study evaluated the efficacy and safety of belimumab in 10 large

academic clinical practices and for the first time it assessed these parameters in childhood-onset SLE. The study observed that belimumab is well tolerated and it improved both clinical and laboratory outcomes in patients with SLE at 6 months across all racial and ethnic groups. Similar improvement is observed among patients with childhood-onset SLE too. In this case, about 35% of patients were able to discontinue steroid treatment after the belimumab therapy (45). A recent study tried to evaluate the cost-effectiveness of belimumab in the Italian context and in patients with a high level of disease activity. This study showed that belimumab is cost-effective, in terms of both ICER (Incremental Cost-Effectiveness Ratio) and ICUR (Incremental Cost-Utility Ratio) (46).

A bird's eye on new therapies

Atacicept

The APRIL-SLE randomised trial looked into efficacy and safety of Atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus. No difference between atacicept 75 mg and placebo for flare rate or time to first flare were observed; while atacicept 150 showed benefit, but the arm was discontinued because of safety reasons. Both atacicept doses were associated with reductions in total Ig levels and antidsDNA antibodies, and increases in C3 and C4 levels (47).

Blisibimod (A-623)

The phase II PEARL-SC study identified a safe, well-tolerated, efficacious and convenient dose of blisibimod (200 mg QW), it established a patient population likely to benefit from blisibimod therapy ('severe' SLE: SELENA-SLEDAI ≥10 and receiving GC) and it defined the end points to be evaluated in a Phase III trial (48).

Bortezomib

In an open-label study, Alexander *et al*. (49) observed that Bortezomib, induces clinically relevant plasma cell (PC) depletion in patients with active, refractory sistemic lupus erythematosus. In particular, upon proteasome inhibition, both disease activity as serum antibody levels, upon proteasome inhibition, declined. However, the authors observed that Bortezomib significantly reduced the numbers of peripheral blood and bone marrow PCs (~50%), but their numbers increased between cycles.

Conclusions

The 2015 yielded new and interesting data regarding the multifaceted aspect of the disease; the most relevant data regarding disease pathogenesis, clinical and laboratory aspects, comorbidities as well as treatment novelties have been summarised here. Far from being exhaustive, this review represents a bird's eye on the recent literature on SLE aimed at soliciting interest and encouraging the reader to go into depth to these selected topics.

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