

One year in review 2015: systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus is a multiorgan autoimmune disease with a highly variable clinical course, typically involving women in childbearing age. At present, many aspects of its pathogenesis still remain unclear. Moreover, although a significant increase of patient survival has been observed in the last decades, morbidity and mortality remain high. Finally, SLE impacts negatively on the health-related quality-of-life of patients. Therefore, multiple aspects of SLE still remain challenging and it continues to be the object of both clinical and translational clinical research. Herewith, we provide a critical digest of the recent literature on this topic.

Introduction

Systemic lupus erythematosus (SLE) is a protean multiorgan autoimmune disease, more prevalent in African-Americans than in Caucasians, typically involving women in childbearing age (1, 2).

SLE may affect different organs and organ systems with a highly variable course, in which periods of quiescence are alternating with periods of disease activity. It is associated with the development of irreversible organ damage, both related with disease activity, with therapies and with comorbidities. Data from the literature show that a control of disease activity, a more careful use of glucocorticoids (GC) and an improved management of comorbidities can reduce damage accrual.

Over the decades a sharp increase of patient survival has been observed, mostly related to a better knowledge of the pathophysiology of the disease itself and to subsequent advances in therapeutic strategies (3).

However, morbidity and mortality in SLE remain high and many aspects of its pathogenesis still remain unclear; moreover, it has been shown to negatively impact the health-related qual-

ity-of-life (HRQoL) of patients (particularly owing to the presence of pain, or the onset of fatigue, fibromyalgia or depression) (4).

The patient's perspective, in particular, has gained a central role in the management of SLE; therefore, validated patient self-report questionnaires should be administered during the routine assessment of SLE patients, to deepen the global evaluation of the disease obtained from the already well known indices used by physicians to measure SLE activity and damage (5).

Therefore, multiple aspects of SLE still remain challenging and it continues to be the object of both clinical and translational clinical research.

Herewith, we provide a critical digest of the recent literature on this topic. We performed a medline search of English language articles published from the 1st January to 31st December 2014 using the following key words: systemic lupus erythematosus, pathogenesis, diagnosis, clinical manifestations, biomarkers, ultrasonography, magnetic resonance imaging, clinimetry, patient reported outcome and treatment. We reviewed all the articles and selected the most relevant papers.

Pathogenesis

In the last year, novel aspects emerged on disease pathogenesis; in particular, very interesting findings are related to the following issues.

Environmental factors

Female sex and estrogens have been considered a risk factor for SLE development. Estrogen receptors (ER) polymorphism rs9340799 G/A was associated with SLE (6). Besides, an increased activation of type a ER in SLE patients was associated with down-regulation of DNA-methyl-transferase 1, thus determining DNA hypo-methylation in CD4⁺ T cells; hypomethylated genes in SLE were shown to be involved in

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different processes, such as leukocyte interaction with endothelial cells and inflammatory response (7).

Genes

Genes coding for the core phagocytic oxydase proteins of nicotinamide adenine dinucleotide phosphate-oxidase (NADPHO) (previously identified as a SLE risk gene) have shown several polymorphisms, that seem to be associated with the onset of SLE in different ethnic groups (8).

Human leukocyte antigen (HLA) system, whose genes are located in chromosome 6, is a key mediator of inflammatory and immune reactions: HLA-DRB1 was proven to be associated with SLE, with the most significant association being mapped in amino-acid position 11, 13 and 26 (9); a recent meta-analysis showed that also HLA-G genes seem to be associated with SLE (10). Different molecules can influence the HLA system, such as leucocyte immunoglobulin-like receptor A3, whose gene expression was increased in a subgroup of SLE patients, being possibly related to aberrant immune activation and autoimmune susceptibility (11).

A recent meta-analysis was conducted to clarify the associations between the vitamin D receptor gene polymorphisms and SLE using allele contrast and the recessive, the dominant and the additive models. The results showed that the BsmI and FokI polymorphisms seem to be associated with an increased risk of SLE, especially in the Asian population. However, further studies are needed to confirm our results (12).

Innate and acquired immunity

As a part of the innate immunity, also natural killer cells (NK) seem to be involved in the disease pathogenesis, usually with a reduction of their number and an increased expression of surface inhibitory receptors; their role in the disease pathogenesis was confirmed by the detection of a new class of auto-antibodies (anti CD94/NKG2A and CD94/NKG2C) targeting lectin-like NK-cells receptors, that seemed to interfere with HLA-E mediated regulation of NK cells (13).

Differentiation from monocytes to macrophages in SLE patients was found to

be different in terms of gene expression from healthy controls, with a distinguishable expression of genes involved in the immune system processes and, particularly, in signal transduction (14). Macrophage migration inhibitory factor (MIF) is known to play a pivotal role in the activation and the migration of macrophages at the inflammation site; the presence of some MIF genes polymorphisms (794 CATT5-8 and 179C>G) could participate to the overexpression of this process (15). Moreover, macrophage polarisation to the M2b profile (subset of alternatively activated macrophages, elicited by interleukin (IL) 1 receptor ligands, immuno-complexes or lipopolysaccharide), typically infiltrating the kidneys in SLE mice models, was shown to be influenced by microRNA (miRNA) expression, changing over time: first controlling signalling pathways, then influencing the physiological functions of cell cycle and cell proliferation (16).

Also, the leptin pathway could have a role in SLE pathogenesis, being responsible of an increased phagocytosis of apoptotic bodies by SLE macrophages (17).

Finally, Li *et al.* observed that an aberrant activated autophagy in macrophages (associated with an increased expression of autophagy related genes in the splenic and renal macrophages) contributed to the pathogenesis of murine lupus possibly via promoting the production of proinflammatory cytokines tumour necrosis factor (TNF- α) and IL-6. Therefore, the inhibition of autophagy might represent a novel regulation strategy for excessive activation of proinflammatory macrophages and a new therapeutic regime for SLE (18).

Also cytokines can influence SLE onset and progression. IL 1 is a well-known promoter and modulator of either inflammatory and immunologic events and its activity is counteracted by specific antagonists competing for receptor binding (such as IL1 receptor antagonist - IL1RA). IL1 levels are increased in SLE patients, and two meta-analysis confirmed the association of its higher levels and some polymorphisms in the genes coding both for IL1RA and IL1R (6).

On the other hand, IL37 levels could be increased in SLE patients, with possible release in the blood stream by peripheral blood mononuclear cells in a positive feedback loops; it might act as a possible regulator of pro-inflammatory cytokines, such as IL1beta, TNF- α and IL 10 (19).

A meta-analysis showed soluble form of cGMP dependent protein kinase polymorphism rs7897633 and purine nucleoside phosphorilase rs1049564 polymorphism to be associated with increased interferon (INF)- α production in SLE. Induction of IFN genes is also modulated by the family of IFN-regulatory factors (IRF), with IRF2 being considered as a negative regulator: a GWAS performed by Kawasaki *et al.* showed that SNP rs13146124, rs62339994, rs66801661 of IRF2 gene were associated with SLE (20).

IFN activation is also strongly associated with changes in B cells lymphopoiesis, through IFN-induced upregulation of BAFF (B cell activating factor), a cytokine involved in the tolerance of B cells; Palanichamy *et al.* showed that bone marrow neutrophils of SLE patients were primary IFN activators, thus providing molecules and signalling mediators involved in B cells development and survival (21).

Regarding the T cell compartment, IL-2 is produced by activated T cells, being a growth factor for conventional CD4⁺ and CD8⁺ T cells, crucial for maintaining their self tolerance. It was shown to reduce the production of CD4-CD8- T cells in a mouse model of SLE, resulting in an improvement of lymphadenopathy, skin and lung inflammation (22).

A recent study on CD4⁺ T cells of SLE patients showed an overexpression of integrin alpha L-chain (ITGAL), perforin 1 (PRF1), and CD70 in SLE CD4⁺ T cells. Further studies are needed to better clarify the possible associations between such alteration and clinical and serological parameters typical of SLE (23).

Cellular signalling mediated by JAK/STAT (Janus kinase/signal transducer and activation of transcription) pathway seems to be involved in SLE pathogenesis. Its activity is regulated

by the suppressor of cytokine signalling 1 (SOCS1), which was proven to be less concentrated in SLE patients compared to controls; besides, the lack of this suppression seems to correlate with disease activity (as measured by SLEDAI score) (24). Finally, inside the STAT pathway, STAT4 gene polymorphism rs7574865 was shown to be associated with the secretion of high levels of INF γ in SLE (25).

Specific organ damage

The kidney is one of the most frequently targeted organs in SLE, with specific podocyte alterations related to proteinuria and with different classes of lupus nephritis (LN) (26). Different gene polymorphisms could be associated with an increased risk of this manifestation, such as integrin alpha M polymorphism rs1143679 G/A (linked to reduced phagocytosis of complement-coated particles) in Europeans (27), the low affinity receptor for FcY FcYR2A-R/H131 in Caucasians (28) and the chemokine receptor (CCR) 5 Δ 32/W in Africans (29). Neuro-psychiatric SLE (NPSLE) was shown to correlate with increased levels of nitrated nucleosomes, usually released during apoptosis and not efficiently cleared in SLE patients; their levels seem to correlate with anti-Sm antibodies positivity (30). Anti-Sm antibodies, moreover, have been demonstrated at higher levels in the cerebro-spinal fluid of SLE patients with acute confusional state, as anti-N-methyl-D-aspartate receptor NR2 antibodies (31). Antibodies against GABA(B)-receptors, seem to be associated with central nervous system manifestations, thus hypothesising an intratechal production (32).

Joint involvement was found more frequently in SLE patients carrying the lymphotaxin (LTA)-252 A/G polymorphism as well as the tumour necrosis factor alpha (TNF- α) promoter-380 G/A gene polymorphism, which seemed also associated with the presence of oral ulcers and malar rash (33).

Laboratory

Autoantibodies

The association of specific clinical features of SLE with particular subgroups

of autoantibodies has been widely investigated, aiming at a better understanding of its pathogenesis and at predicting the various types of organ damage.

On the basis of the data from the Chinese SLE Treatment and Research group (CSTAR) registry (2104 SLE patients) significant associations were found between anti-Sm antibodies, anti-ribosomal RNA-protein (rRNP) antibodies and malar rash, between anti-U1 small-nuclear RNA-protein (anti-U1snRNP) antibodies, anti-SSA antibodies and pulmonary arterial hypertension (PAH), between anti-SSB antibodies and haematologic involvement (in particular leukopenia, haemolytic anaemia, and thrombocytopenia) and between anti-dsDNA antibodies and nephropathy. Anti-phospholipid (APL) antibodies seemed generally associated with haematologic involvement (leukopenia, haemolytic anaemia, and thrombocytopenia) and interstitial lung disease (34). Another analysis of 852 patients with SLE seemed to support the association between autoantibody clusters and distinct clinical features, showing a predictive value on the outcome of the disease. Four autoantibody clusters were defined: 1) dsDNA cluster, associated with the highest incidence of renal involvement and a high risk of renal damage, 2) Sm/RNP-cluster, significantly associated with a higher incidence of PAH and Raynaud's phenomenon, 3) anti-cardiolipin autoantibodies/lupus anticoagulant (aCL/LAC) cluster, significantly associated with neuropsychiatric involvement, antiphospholipid syndrome, autoimmune haemolytic anaemia, thrombocytopenia and increased accrual of damage, measured with the SLICC Damage Index, 4) anti-Ro and anti-La cluster, which strangely did not show any distinctive clinical association (35).

A novel ELISA system for simultaneous detection of six subclasses of aPL among SLE patients that was developed in Japan showed that the concentration of anti-phosphatidylserine/prothrombin (aPS/PT) seemed most closely associated with arterial thrombosis, while the concentration of anti- β 2-glycoprotein I (a β 2GPI) appeared most closely relat-

ed to venous thrombosis. Finally, both aCL/ β 2GPI and aPS/PT were independently associated with episodes of recurrent foetal loss (36).

A recent matched case-control study confirmed that an anti-dsDNA surge may predict the subsequent development of a severe SELENA-SLEDAI flare, potentially leading to an hospitalisation within six months, thus confirming the importance of closely monitoring this kind of SLE patients to promptly treat them (37).

Over the years a huge number of candidate SLE biomarkers were reported, but their utility in routine clinical practice has yet to be determined. In 2014 some potential novel biomarkers for SLE have been identified; in particular, autoantibodies against CAF-1, one of the proliferating cell nuclear antigen (PCNA)-binding proteins could represent a useful biomarker for the diagnosis and seemed to be associated with the central nervous system (CNS) involvement, while anti-class I HLA antibodies could be a biomarker for the development of thrombocytopenia and photosensitivity (38, 39).

Anti-GABARb Abs, antibodies against the main inhibitory neurotransmitter in the brain, could represent novel candidate markers for disease activity in SLE because they were exclusive of patients with SLE (when compared with scleroderma, myositis, vasculitis and healthy subjects) and significantly associated with SLEDAI score and with neurological involvement (40).

Moreover, Lauvsnes *et al.* confirmed the potential role of antibodies against the NR2 subtype of the N-methyl-D-aspartate receptor (anti-NR2Abs) as biomarkers of CNS involvement. Indeed, in mice with autoimmune diseases, they were already shown to be associated with neuronal death; accordingly with these preliminary data, SLE patients with these autoantibodies detected in the cerebrospinal fluid showed an hypotrophy of the hippocampal gray matter if compared with SLE patients anti-NR2Abs negative (41).

Complement

A recent work by Li *et al.* showed that the levels of C3d and C4d binding to

peripheral CD4⁺ T and CD19⁺ B lymphocytes (respectively T-C3d, T-C4d, B-C3d, B-C4d) were significantly higher in SLE patients than in patients with other diseases and healthy controls. In particular, T-C4d and B-C4d were significantly associated with SLE disease activity, thus demonstrating that complement activation products binding to lymphocytes can reflect the disease activity of SLE and could be used as biomarkers for SLE (42).

T lymphocytes

On the other hand, many studies have demonstrated quantitative and/or qualitative defects of T regulatory cells (Treg: phenotype CD4⁺CD25^{high}FOXP3⁺) in lupus patients and in 2014 Tselios *et al.* found that Treg showed a strongly inverse correlation with disease activity (SLEDAI) in the long term, thus representing a potential BM for the assessment of disease activity in SLE by longitudinal measurements (43). Among the overall population of Treg, a novel subset that does not express CD25 surface molecules may be a marker for high disease activity and lupus nephritis (LN), potentially useful to recognise and monitor SLE patients with renal involvement (44).

Biomarkers of lupus nephritis

At present, kidney biopsy remains the gold standard for the diagnosis of LN; the need for non-invasive and more feasible diagnostic tools in this field is therefore crucial. In effect, in 2014 there was a volcanic explosion of new biomarkers of LN. In serum, higher levels of growth arrest-specific protein 6 (a protein involved in granulocyte, platelet and endothelium interactions and implicated in both anti-inflammatory response as well as platelet/leukocytes activation), soluble form of the IL7 receptor, soluble chemokine ligand 16 (able to recruit specific leucocytes to target tissue sites, leading to organ damage and to induction of T cell), osteopontin (an extracellular matrix protein which can work as a proinflammatory cytokine promoting macrophage infiltration, activation, and retention in inflamed tissues), advanced oxidation protein products (generated by

myeloperoxidase in neutrophils due to oxidative stress) and human neutrophil peptides 1-3 (an important part of the innate immune system able to regulate inflammation in different ways) have shown a potential role in predicting the occurrence of a LN flare and could be used to monitor the therapeutic response (45-50). Furthermore, urinary biomarkers are attractive candidates since on the one hand they are relatively easy to measure and on the other hand they specifically reflect the local pathophysiological changes. In urine samples an increase of CXCL10 (a chemokine secreted by IFN- γ stimulated endothelial cells), IL-22 binding protein (a soluble inhibitory IL-22 receptor), adiponectin, β 2-microglobulin (released from immune-related cells such as activated T- and B-lymphocytes and macrophages) and neutrophil gelatinase-associated lipocalin (one of the most robustly expressed proteins by injured kidneys) might be potential biomarkers of renal involvement in patients with SLE, but larger studies are needed to further investigate their diagnostic role (51-55).

Clinical picture

Cardiovascular involvement

Atherosclerosis (ATS) is common in patients with SLE, being associated with a 2–5-fold increased risk of future cardiac, cerebral or peripheral arterial ischaemic events and mortality; moreover, it is a well accepted evidence that cardiovascular (CV) events are the leading cause of mortality in SLE (56). In agreement with these data, SLE patients show a higher prevalence of subclinical carotid and aortic ATS, manifested as intima-media thickening and a higher prevalence of subclinical coronary artery disease manifested as calcifications on computed tomography. Premature aortic stiffness, an early atherosclerotic process, is also common in patients with SLE. Considering that traditional Framingham CV risk factors do not fully explain the excess of the risk observed it is likely that inflammatory and autoimmune mechanism interact with genetic, environmental and treatment-related factors, triggering and perpetuating the vessel wall damage (57). The accelerated endothe-

lial cell apoptosis and the consequent reduced percentage of endothelial progenitor cells seem to play a key role in vascular damage and in subclinical ATS occurrence, thus acting as potential early marker of ATS (58). The diagnosis of peripheral arterial disease, even in asymptomatic patients, seems to be fundamental to prevent future vascular events; in SLE patients the prevalence of a lower ankle-brachial index is higher, but further studies are necessary to correlate this measure with SLE-specific variables (59). SLE patients tend to have an increased intima media thickness and a decreased flow mediated dilatation, associated with both traditional and disease-specific risk factors; in particular it has been demonstrated a link between an autoimmune chronic damage of the arterial wall and ATS, represented by a β 2GPI-specific T cell reactivity (60). A French research has confirmed the increase of arterial stiffness (AS) in SLE patients and the correlation with systolic blood pressure and GC therapy, despite a low risk for CV disease (CVD) according to Framingham score (61). A close link has been found between metabolic syndrome and SLICC/ACR score and AS, supporting the hypothesis that the first one might contribute to the development of an accelerated ATS in SLE patients (62).

A recent study showed that a higher baseline disease damage score and a higher baseline disease activity could be predictors of progression of coronary artery calcium and aorta calcium respectively, both parameters of subclinical ATS (63).

Although several studies have focused their attention on the investigation of underlying mechanism of ATS, data about the application of preventive strategies are still lacking. In SLE patients, indeed, it would be crucial to introduce at least the evidence-based measures to prevent CV risk adopted also in the general population. A regular physical activity, in particular, is a life-style modification that could be able to improve macro- and micro-vascular function, chronic inflammatory markers balance and disease activity (64). Finally, recent data from the LUMINA cohort showed

that a therapy with statins was associated not only with the improvement of the lipid profile, but also with a significant decrease in the disease activity, measured by the systemic lupus activity measure-revised (SLAM-R) index (65).

Kidney involvement

LN is one of the most severe manifestations of SLE and one of the main predictors of a poor prognosis. Accurate epidemiologic data about LN are still lacking, but current studies report a lower cumulative incidence in Caucasians than Asians, Africans and Hispanics, thus confirming a possible role of some environmental factors in its pathogenesis. In China, in particular, a decreasing incidence of LN going from the North to the South of the Country has been observed (66).

Recent data have confirmed that the presence of chronic lesions on initial biopsy and suboptimal response to therapy are critical prognostic factors for long term renal outcome (67). LN, indeed, represents a significant risk for an earlier development of a chronic kidney disease and is associated with a higher rate of cardiovascular events (68). Some different renal patterns of injury have been identified [mesangial, endothelial, epithelial (podocytes), tubulointerstitial, vascular], differing for their clinical presentation and outcome. In particular, podocyte involvement was common, but it may act as a real distinct entity called "podocytopathy", without any evidence of typical immune complex deposits but with an extensive podocyte effacement (69). Moreover, some patients may present a non classical glomerulonephritis with "scanty immune deposits", indicating a particular kind of renal lesion with little or absent immunoglobulins and not necessarily lesions with necrosis or crescents. The presence of these deposits are associated with a more severe kidney damage and a worse renal outcome (70). A non-inflammatory necrotising vasculopathy (NNV) may be present among the different spectrums of LN, being characterised by a necrotising damage in the pre-glomerular arterioles, with a minor involvement of the interlobular arterioles. Recent data have shown that up

to 6% of LN biopsies may reveal NNV, indicating that this entity is not so rare; it could be of great interest to discover it, owing to its strong correlation with active clinical status and proliferative glomerular lesions (71).

Taking into account those patients with LN evolved in renal failure (RF), a retrospective activity analysis showed decreases in disease activity from 87.5% to 37.5% in those treated with dialysis and from 92.8% to 28.6% in those who underwent transplantation. Serological markers and haematological BILAG activity were the predominant indicators for post-RF lupus activity. Further studies are needed to better clarify whether the measured activity derived from an intercurrent process or was intrinsic to the renal failure itself (72).

Nervous system involvement

Nervous system involvement is one of the most serious manifestations of SLE, that may target both central, peripheral and also autonomic section, being associated with a bad prognosis. The clinical presentation may be very heterogeneous, including both neurological and psychiatric events (headache, psychosis, seizures). Data about survival in neuropsychiatric SLE (NPSLE) are scarce and conflicting: the most frequent cause of death seem to be infections and SLE itself (73). In SLE patients psychiatric symptoms like depression and suicidal ideation might be associated with the physical disability (linked to fatigue, joint pain, treatments) and with a poor prognosis in the cases of a more severe disease. SLE activity on central nervous system seems to correlate with mood disorders (74, 75).

Data from a 25-year study of 2097 SLE patients show that the small fibre neuropathy (a subtype of neuropathy not included in the ACR NPSLE case definitions) is significantly frequent and seems to correlate with higher disease damage scores (76).

A recent study showed a significant prevalence of cognitive impairment both in SLE patients without APL autoantibodies and in patients with APL without a diagnosis of SLE, thus confirming the association of both SLE

and APL with possible neurologic compromise, even if the pathological mechanisms are still far to be elucidated (77).

Imaging

Joints

Contrast-enhanced magnetic resonance imaging (MRI) of the hand and wrist performed in 34 SLE patients with hand arthralgia or arthritis showed that almost all SLE patients had erosions at the wrist, while more than half of them had erosions at the metacarpal heads; furthermore a low-grade MRI-synovitis, which may offer an explanation for the high prevalence of arthralgias, was common in lupus patients (78). Echographic signs of joint inflammation at the hands or the wrists were found in more than 50% of SLE patients, also without a history of musculoskeletal involvement (79). Iagnocco *et al.* confirmed a high prevalence of ultrasound inflammatory joint abnormalities (joint effusion, synovial hypertrophy and local pathological vascularisation-power Doppler) in hand, wrist and especially foot joints of SLE patients (80).

Central nervous system

It is well known that MRI is usually considered the gold standard imaging method in the evaluation of cerebral lesions in patients with SLE. The role of antiphospholipid antibodies as risk factor for the occurrence of cerebral lesions was confirmed in a recent study that showed a significantly increased prevalence of pathological brain MRI findings as infarctions (large or localised), anterior basal ganglia lesions or stenotic arterial lesions in SLE patients with a secondary antiphospholipid syndrome (APS) (81). Moreover, Futatsuya *et al.* found that the presence of lacunar and/or localised cortical infarcts itself on initial MRI scans, performed as screening in SLE patients younger than 50 years, might be an independent predictor of development of new brain lesions at 12–24 months (82). On the other hand, even in SLE patients with NP manifestations, conventional MRI may not provide an explanation for signs and symptoms; therefore, techniques of more advanced neuroimaging

may be indicated. Zimny *et al.* showed that in SLE and NPSLE subjects with a normal plain MRI, advanced MRI techniques were capable of an *in vivo* detection of complex microstructural brain damages regarding neuronal loss, mild hypoperfusion and white matter disintegrity. In particular, MR spectroscopy and diffusion-tensor imaging seemed to show the highest usefulness in depicting early changes in normal appearing grey and white matter in SLE/NPSLE patients; the area of the posterior cingulate region, part of the limbic system involved in the memory and learning processes, seemed to show the most pronounced alterations, with abnormalities more pronounced and widespread in NPSLE patients compared to SLE subjects without a neurological involvement. Very interestingly, a profound damage of commissural and many association tracts have been shown as the major difference between SLE patients with or without neurological symptoms. Finally, this study confirms that in NPSLE patients perfusion deficits seem to participate significantly in the development of neuronal damage (83).

Heart

In a study on asymptomatic patients with SLE, sarcoidosis, systemic sclerosis, rheumatoid arthritis and inflammatory myopathies having a normal echocardiography after a recent diagnosis of left bundle-branch block (LBBB), cardiovascular MRI documented both acute and chronic cardiac pathologies, with a major prevalence of myocarditis (33% of SLE patients, with histological characteristics of acute autoimmune myocarditis confirmed in half of them). After administration of corticosteroids and Azathioprine, the LBBB disappeared in all SLE patients with myocarditis and the cardiovascular MRI was normalised. These data show the usefulness of MRI as an adjunct to the conventional diagnostic CV workup in detecting signs of cardiac disease involvement, even if subclinical (84). Moreover, a study conducted by Mavrogeni *et al.* showed that in patients with connective tissue diseases (SLE, inflammatory myopathy, sarcoidosis, systemic sclerosis, rheumatoid arthritis, small-

vessel vasculitis) with cardiac symptoms and normal echocardiography, the cardiovascular MRI could disclose different patterns of myocardial lesions, in particular myocarditis, diffuse sub-endocardial vasculitis, and myocardial infarction (85).

Clinimetrics

It is well known how the perception of disease activity of SLE patients tends to be discordant from that of their physicians. From this assumption, the need of patient reported outcomes (PRO) in the management of SLE patients has gained a central role (86). In the field of the quality of life (QoL), Oude Voshaar *et al.* demonstrated that in SLE there was a link between the Health Assessment Questionnaire (HAQ) disability index (DI) and the Short Form 36 (SF-36) physical functioning scale (PF-10), or rather it was possible to convert HAQ DI to PF-10 scores and vice versa by conversion tables (87). Urowitz *et al.* proved that in patients with early lupus the SF-36 seems to be sensitive to change, considering that patients starting with an active disease, after an adequate treatment, in the first 2 years from enrolment showed an improvement in all 8 subscales, with no subsequent changes (88).

From the longer LupusPRO, a new and brief PRO instrument has been validated: the Lupus Impact Tracker (LIT). It can be used routinely in clinical practice by patients and physicians to assess and monitor the impact of SLE because it's reliable and responsive to changes. The 10 LIT questions included the concepts of cognition, lupus medications, physical health, pain/fatigue impact, emotional health, body image, and planning/desires/goals (89). SLE is a well known risk factor for depression and anxiety, as confirmed in a Chinese cohort of SLE patients, in which psychiatric disorders such as anxiety and depression (evaluated by self-rated scales for anxiety - SAS and depression - SDS), together with disease activity, influenced significantly patients' QoL (90). These data highlight the importance to focus also on psychosocial factors when aiming at improving the QoL of lupus patients.

SLE is usually associated with the onset of irreversible organ damage, mainly related to disease activity and/or side effects of the drugs used to treat the disease (91). Therefore, quantifying organ damage has become a relevant issue of outcomes research. The measurement of damage due to SLE traditionally relies upon the validated Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), a physician's assessment index (92). Validated patient-reported measures of damage derived from SDI are the Lupus Damage Index Questionnaire (LDIQ, 56 items) and the Brief Index of Lupus Damage (BILD, 28 items) (93, 94). In 2014 the BILD, shorter and more feasible than LDIQ has been tested longitudinally and has confirmed its predictive validity, also as a strong predictor of mortality (95). Furthermore, a self-administered BILD (SA-BILD) has been validated in a predominantly African American cohort of US SLE 711 patients and it has been shown to have a good agreement with the SDI (96).

Therapy

Traditional drugs

Hydroxychloroquine (HCQ), chloroquine (CQ) and quinacrine have been used for a long time as disease-modifying anti-rheumatic agents in the treatment of SLE and other autoimmune diseases and they are still widely prescribed. It has been described that they prevent lupus flares and increase long-term survival of SLE patients, probably thanks to their ability to downregulate the production of TNF- α and other proinflammatory cytokines. *In vitro* studies showed that CQ seems to interfere with the expression of TNF- α probably by affecting the cellular lysosomal acidification. Moreover, a recent study has confirmed this inhibitory effect even when TNF- α induction is enhanced by IFN α , an expected situation in most of SLE patients. CQ treatment seems to inhibit *in vitro* the induction of TNF- α and STAT4 in stimulated monocytes, caused by IFN α . Even the effects of antimalarials (AM) on SLE could be influenced by the IFN α serum levels of patients (97).

The adherence of SLE patients to the suggested therapeutic scheme of AM is a very sensitive issue. In a recent Dutch study it was observed that their use has improved in recent years, but it is not yet optimal. Discontinuation due to side-effects is the most reported reason for non-use, although infrequently occurring. Non use of AMs was significantly but not independently associated with a longer disease duration, although a trend for such an association was found. This association probably reflects the non-use of AMs in the past, and the increased use of AMs in recent years. Another explanation may be that in some cases a prolonged use of AMs may be associated with adverse events, such as in patients with AM related retinopathy and cardiomyopathy. These data show that, despite increased awareness of the importance of AM treatment in SLE, there is still room for improvement. Daily dosages of HCQ often exceeded those recommended from guidelines, but were generally well-tolerated (98).

The therapeutic role of IVIG in SLE has not been studied in RCTs (with the exception of a small RT of low dose IVIG in lupus nephritis) but mainly in observational studies or case reports. They interact with innate and adaptive arms of the immune system, interfering with the establishment of the immune homeostasis that is usually compromised in rheumatic diseases.

In a recent retrospective observational single-centre study, 52 SLE patients, who were administered to at least one cycle of high dose IVIG (0.4 g/kg/day for 5 days per cycle) from 2001 to 2011, have been studied; they were treated with IVIG owing to concurrent infections and persistent disease activity or a disease activity refractory to standard therapy. The disease involvements were predominantly cutaneous, hematologic, cardiac and neuropsychiatric. This study emphasises that IVIG treatment is quite effective, with complete remission in 37% of patients with active disease and concomitant infections and 30.7% in patients with active disease refractory to standard therapy. However a less efficacy in skin involvement and a greater one in hemato-

logic involvement were observed. Patients with concomitant infections who experienced any benefit from IVIG had a longer time free from relapse compared to those without, thus confirming the therapeutical indication of IVIG in challenge situations, such as SLE and concomitant infections (99).

Kidney involvement

To date, the use of DMARDs in association with steroids for the induction of remission remains the treatment of choice of Lupus Nephritis (LN), to preserve renal function and improve overall survival.

High-dose or shorter duration lower-dose regimen of cyclophosphamide (CYC) have proved efficacy in inducing remission, despite serious side effects and risk of relapse. Therefore further trials were directed to find an ideal dosage and duration for IV CYC treatment. Zhang *et al.* reported a prospective 1-year follow-up study comparing the efficacy and safety of two CYC regimens, short interval lower-dose (SILD) (12 fortnightly IV CYC pulses at a fixed dose of 400 mg for 6 months and followed by 6 monthly pulses) *versus* high-dose (HD) (6 monthly pulses at a dose of 500 mg/m² of body surface area, followed by 2 quarterly pulses whose doses were increased by 250 mg according to the white blood cell count). The 79.4% of patients in the SILD group and 78.5% in the HD group ($p=0.867$) achieved the primary end point in terms of complete and partial remission (CR/PR), with similar incidences and mean time in the two groups. Side effects were less common in the SILD group, especially as regards menstrual disturbances and gastrointestinal adverse effects (nausea or vomiting), with statistical significance (100).

Another attempt was made by the Dutch Working Party on SLE that investigated the effects of induction therapy with short-term high-dose IV CYC followed by mycophenolate mofetil (MMF) on renal function, mortality, adverse events and quality of life in patients with class III or IV LN. Seventy-one patients were all treated with 750 mg/m² IV CYC monthly for six pulses, followed by MMF (1 g twice daily) for 18 months

and then with azathioprine (AZA) (2 mg/kg/day) plus oral prednisone. During a mean follow-up of 3.8 years, this regimen seems effective in preventing renal relapses, ESRD and mortality and it could be considered in those patients who had an exacerbation or who have not achieved remission with MMF. Serious infections occurred in about 21% of patients (more than 50% experienced an herpes zoster virus infection); 2 patients died (one for sepsis and one for anaplastic T-cell lymphoma) (101).

An observational study evaluated the recovery time of proteinuria in the course of standard of care (steroids plus MMF, AZA, Methotrexate or CYC), in 212 patients with LN of the Toronto Lupus cohort, from 1970 to 2011 ("recovered" was considered a proteinuria <0.5 g/24 h). In the analysis 28% of the patients recovered from proteinuria within 1 year, 52% within 2 years and 74% within 5 years, underlining how achieving a CR on standard of care could be very difficult and slow. Moreover the time appears adversely influenced by the baseline level of proteinuria, low levels of complement, male sex and disease duration >5 years at the renal flare (102).

Calcineurin inhibitors have a proven short-term immunosuppressive efficacy as treatment of proliferative and membranous LN, for a direct action on podocytes. A recent Chinese study has demonstrated the efficacy of tacrolimus in reducing proteinuria in patients with membranous LN, with a response rates after 12 and 24 months of 66.7% and 80.0%, and in those with proliferative LN who did not respond despite conventional immunosuppressive treatment, with a response rates of 60.0% and 90.0% after 12 and 24 months respectively (103).

The efficacy of tacrolimus (Tac) in the induction of remission of active LN (class III/IV/V) after 6 months of therapy was confirmed in a randomised control trial by Mok *et al.*, demonstrating a non-inferiority to MMF. After a follow-up of 5 years with AZA maintenance therapy, they reported, as long-term outcome, a non-significant trend of higher incidence of renal flares and renal function decline with the Tac regimen (104).

The recent literature has debated on the doses of prednisone to be used in LN. A comparative study between two different protocols of induction therapy was conducted, the one using medium doses of prednisone (15–30 mg/d, then tapered, depending on LN class) associated with methyl-prednisolone pulses, immunosuppressants (mainly CYC) and hydroxychloroquine, the other using high doses of prednisone (1 mg/kg/d with variable duration and tapering scheme) associated with immunosuppressants. The comparison between the effects of high *versus* medium doses of prednisone in the induction therapy of LN shows a superiority of the second group in terms of efficacy and lower toxicity, although the two groups of patients was heterogeneous for clinical characteristics and concomitant medications (105).

Rituximab

Moroni *et al.* designed a non-randomised controlled study comparing treatment of LN with Rituximab *versus* MMF *versus* CYC pulses. After three months from the beginning of the induction therapy, renal response occurred with the same frequency in all groups. At 12 months, in maintenance therapy with MMF, AZA or Cyclosporine A (CyA), a CR was present in 70.6% of patients on RTX, in 52.9% on MMF, and in 65% on CYC. Note that 12-month clinical renal remission (complete or partial) was achieved in all patients treated with RTX. Although the majority of patients treated with RTX entered the study at the diagnosis of a new renal flare and, as a consequence, had a longer disease duration, higher activity and chronicity indexes at renal biopsy than the other two groups, RTX has proved at least as effective as MMF and CYC in inducing remission, with a good safety profile, confirming the possibility of its use in cases refractory or intolerant to conventional therapies (106).

Moreover, a Spanish study suggested that RTX might improve the long-term lipid profile of patients with SLE refractory to standard treatment. This action could reasonably be related with the reduction in the production of autoantibodies and pro-inflammatory cy-

tokines it determines; indeed, IL6, IL1 and particularly TNF- α , seem to be involved in insulin resistance, to interfere with lipoprotein lipase and to increase the de novo synthesis of very low-density lipoproteins (107).

Belimumab

Recently it has been demonstrated that belimumab maintains a profile of safety and efficacy, in combination with steroids and DMARDs, in the long term in patients with moderate-severe SLE disease activity. The efficacy has been explained in reduction of flares occurrence, steroid dose and the title of anti-dsDNA (108).

In two placebo-controlled trials conducted in patients with active, autoantibody-positive SLE (BLISS-52 and BLISS-76), belimumab plus standard therapy resulted in significantly higher SLE Responder Index (SRI) response rates at 52 weeks compared with standard therapy plus placebo, both in greater reductions in SLE disease activity with treatment (clinically meaningful improvement in SELENA-SLEDAI, no worsening of disease measured by BILAG organ domain score) and improvements in health-related QoL and fatigue measures (109).

An additional *post hoc* analysis in these studies was also performed, to assess the type of response, irrespective of treatment assignment, among SRI responders and non-responders. SRI responders reported greater improvements from baseline in a range of clinical, laboratory and health-related quality of life measures compared with non-responders, highlighting that these patients achieved a global benefits (110).

Moreover, a recent study evaluating the effectiveness of belimumab in Italian SLE patients with active disease, anti-ds-DNA autoantibodies and hypocomplementemia, despite standard of care, has confirmed that this drug is cost effective in this kind of patients, being the main drivers of cost-effectiveness the treatment efficacy and the discontinuation rate (111).

Epratuzumab

Epratuzumab, a humanised monoclonal antibody targeting CD-22 recep-

tors on B lymphocytes, has emerged as a novel therapeutic alternative for SLE patients.

EMBLEM is a Phase IIb multicentre 12-week RCT that evaluated its efficacy and safety in patients with moderate-to-severe SLE disease activity, through the index BICLA, including the assessments of BILAG -2004, SLEDAI-2K and physician global assessment of disease activity (PGA), as well as to identify appropriate dosing regimens for epratuzumab phase III RCTs. As primary endpoint, the rate of responders at week 12 according to BICLA was higher, in a pairwise analysis of the arms of the trial, in patients receiving a cumulative dose of 2400 mg. This drug was well tolerated and its safety profile was confirmed by the same incidence of adverse events between all the arms of the trial, unrelated to epratuzumab dose. At week 12, moderate reductions in B-cell counts were observed in all groups, but no decreases in immunoglobulin levels outside normal ranges (112).

The ALLEVIATE trial provided preliminary evidence of the efficacy and safety of epratuzumab in patients with SLE; in particular, it demonstrated clinically meaningful and sustained improvements in PGA, Patient Global Assessment, HRQoL together with a reduction in GC doses (113).

Drug interactions, side effects and induced damage

Ruiz-Arruza *et al.* confirmed that in patients with SLE damage is proportional to the cumulative dose of GC and to the average daily dose, given as a threshold for damage accrual after 5 years of follow-up the average doses of prednisone >7.5 mg/day. Methylprednisolone pulses are not related to new damage accrual in these patients (114). Finally, a secure relationship between disease activity and the development of lymphoma in patients with SLE has not been proved, not even a clear risk in medication exposures, since a case-cohort analysis showed that many lymphomas were not exposed to any immunosuppressive therapy before the onset of malignancy. However a higher proportion of SLE patients who developed a lymphoma were treated with CYC

compared with cancer-free controls (although lymphomas among subjects exposed to CYC was relatively small) as well as with higher cumulative steroid use (115).

Treat to target

Several observational studies have evaluated the use of the well known therapeutic resources for SLE patients and their better management in the recent years, observing a decrease in disease activity during the follow-up, an improvement of clinical and patient-reported outcomes and participation in the labor, as well as a decline in health-care use. An earlier referral to a rheumatologic care and a faster treatment modification have represented significant aspects in assuring this improvement (116).

As in rheumatoid arthritis, the principle of “treat to target” has been applied in SLE, in order to yield superior outcomes in terms of clinical course, long-term damage and functional status. Through systematic literature reviews, a large task force of multispecialty experts accompanied by a patient representative, have developed 11 recommendations for the treatment of SLE, especially about targeting remission, preventing damage and improving quality of life. From this first step of a process that will be surely long and complex, some primary issues are arisen: (i) the therapeutic approach of SLE should entail a range of targets that all must be taken into account, (ii) should be multidisciplinary, (iii) patients should be monitored regularly and (iv) at least one validated disease activity measure should be regularly assessed (117).

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