Review

One year in review 2018: systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a systemic autoimmune condition characterised by a wide spectrum of clinical manifestations, partly related to the disease itself, but also linked to its comorbidities and drugs adverse reactions. Following the previous annual reviews, we focused on new insights in SLE clinical features, pathogenic pathways, biomarkers of specific organ involvement and therapeutic strategies. We finally concentrated on SLE aspects that could significantly influence patients' quality of life and that need to be investigated in detail through the development and validation of disease-specific patient-reported outcomes.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with clinical and serological heterogeneity. In order to find recent and up-to-date developments regarding its pathogenesis, diagnosis, treatment and comorbidities, it was performed a MEDLINE search of English language articles published from the 1st January to the 31st December 2017 using MESH terms and free text words for the following search keys: systemic lupus erythematosus AND pathogenesis, biomarkers, clinical manifestations, malignancies, infections, osteoporosis, therapy, quality of life and patient-reported outcomes. Reviews were excluded from this work, as well as only papers about adult SLE were considered. After reviewing all the articles, the most relevant ones were selected. The aim of this one year in review, following the path set last year (1), is to provide a helpful anthology on the latest findings about SLE.

Pathogenesis
Innate and acquired immunity
Interferon (IFN)-α has a known strategic role in SLE pathogenesis and it is the main product of plasmacytoid dendritic cells (pDCs). Usually IFN-α production is induced in response to single-strand RNA and to bacterial/viral DNA by, respectively, Toll-like receptors (TLR) -7 and -9. INF-α production in SLE is increased by TLR7 stimulation of pDCs; moreover, TLR7 expression is increased in pDCs' endosomes/lysosomes from SLE patients compared to healthy controls. These findings suggest the importance of TLR7 pathway in IFN-α-mediated SLE pathogenesis (2).

A study compared serum mRNA levels of TLR9, transforming growth factor β (TGF-β) and platelet-derived growth factor B (PDGF-B) in SLE patients and healthy controls, showing that TLR9/TGF-β/PDGF-B pathway is excessively activated in SLE patients' plasma. In addition, an in vitro study indicated that this pathway can induce mesangial cells over proliferation, suggesting a possible role of TLR9/TGF-β/PDGF-B pathway in SLE kidney involvement (3).

A study conducted by Elloumi et al. pointed out the importance of TLR-4 expression analysing, with immunohistochemical staining, the biopsies from lupus nephritis (LN) and from chronic cutaneous lupus. In these patients, TLR-4 expression in biopsies from kidney and skin was higher than controls, highlighting a possible crucial TLR-4-mediated pathogenic pathway in LN and in chronic skin manifestations (4).

Basophils are involved in the pathogenesis of several skin diseases. Pan et al. studied skin biopsies from SLE patients and found a significant presence of basophils while these cells were not present in tissues from healthy controls. Moreover, using an in vitro migration study of peripheral blood basophils and an immunohistochemical

examination of skin biopsies, it was concluded that Chemokine Receptor 1 (CCR1) and Chemokine Receptor 2 (CCR2) mediate basophils recruitment in SLE skin lesions (5).

Apoptosis, apoptotic microparticles (MPs) and neutrophil extracellular traps (NETs) formation (named NETosis) are a key aspect in SLE pathogenesis, in particular NETosis has an important role in LN. A recent study showed that MPs deriving from patients with active LN have higher levels of acetylated chromatin and more capabilities in NETs formation in comparison with MPs from patients with inactive LN, without LN and healthy controls. Therefore, acetylated chromatin seems to be a strong stimulus to trigger NETosis in SLE neutrophils. Furthermore, this study demonstrated that NET formation under MPs triggering is quicker and does not need an additional process driven by reactive oxygen species (ROS) formation (6).

With regard to the acquired immunity counterpart, Vitales-Noyola *et al.* analysed CD4$^+$ CD69$^+$ cells, a peculiar regulatory T (Treg) cells subset which has an important immunosuppressive effect. It was demonstrated that in SLE the proportion of circulating CD4$^+$ CD69$^+$ Treg cells is increased compared to controls and that these cells have a reduced capability to decrease autologus T-lymphocyte activation and cytokine output. Thus, the increased production of CD4$^+$ CD69$^+$ Treg cells could contribute to creating a defective over-immunoreactivity in SLE patients (7).

Genetic and epigenetic factors
An American work explored the relationship between gene expression ad innate immunity activity analysing the role of type I IFN in inflammasome activity. It was observed that inflammasome activity and its IFN-regulated genes in monocytes from SLE patients were increased compared to controls. High inflammasome IFN-induced activity takes place through up-regulation of Interferon Regulatory Factor-1 (IRF-1) and could have an important role in SLE inflammation and organ damage (8). Another study compared NCF1 polymorphisms of 973 Swedish SLE

patients and 1301 healthy controls, correlating their expression with ROS production and IFN-I-regulated gene expression. The NCF1-339 T-allele was more frequent in SLE and associated with reduced extracellular ROS formation and an increased IFN-I-regulated gene expression. Moreover, the NFC1-339 T-allele was associated with a younger age at SLE diagnosis (30.3 years *vs.* 35.9 years) (9).

Concerning gene expression and acquired immunity, pre-B Cell Leukemia Homebox-1 (PBX1) is a well known gene associated with SLE and its expression drives the generation of autoreactive T CD4$^+$ cells and the impairment of Treg cells. Interestingly Niu *et al.* showed that PBX1-d, a new splice isoform of PBX1 SLE-associated gene, directly transcripts the T cell activation marker CD44, confirming that PBX1, in particularly its d-isoform, has a primary role in T cell-mediated SLE pathogenesis (10).

Epigenetic pathways take part in SLE pathogenesis and so far, DNA hypomethylation rather than hypermethylation has been explored. A recent study found that hypermethylated CD3Z is associated with a downregulation of CD3ζ-chain, altering T-lymphocyte activity, and it is correlated with a severe SLE presentation, including haemolytic anaemia, thrombocytopenia and proteinuria (11).

Environmental factors
New evidences on the relationship between genetic polymorphisms and environment in contribution to SLE pathogenesis have been published. A Chinese paper found that the polymorphism rs2234693 of Estrogen Receptor alpha gene (ESR1) increases the risk of SLE in smokers patients compared to never-smokers (12).

In another work, single nucleotide polymorphisms (SNPs) were analysed in four vitamin D genes, measuring 25-OH vitamin D blood levels in 436 patients at risk of SLE development. It was observed that hypovitaminosis D and the presence of two copies of the minor allele at rs4809959 of CYP24A1 gene have an additive role in transition to SLE (13).

Biomarkers
A great effort is made every year to try to define reliable biomarkers for SLE: there is the need to find non-invasive and easy-measurable surrogates able to assess disease activity or treatment response or even to suggest an early diagnosis. Thus, several biomarkers have been evaluated, especially regarding renal flares in LN. The continuing growth in biomarkers research has the ambitious goal to provide in future clues for personalised therapeutic regimen selection.

Before approaching the new emerging biomarkers, an interesting help seems to come from the traditional ones. In fact, it has been seen that SLE patients have generally a decreased platelet size compared to healthy controls. This is due to an increased platelet activation; moreover, the reduced platelet volume associates significantly with anti-cardiolipin antibodies (14).

To investigate the clinical value of anti-Sm antibodies in diagnosis and monitoring of SLE, a cross-sectional longitudinal and predictive analysis was performed, showing that 14.8% of anti-dsDNA-negative patients were positive for anti-Sm, and more than half (51.4%) of anti-dsDNA-positive patients were also positive for anti-Sm. Although no correlations with lupus activity were observed in the longitudinal and predictive analysis, a remarkable association was found between anti-Sm and proteinuria, suggesting that anti-Sm monitoring is helpful in SLE patients with active LN (15).

Another interesting finding comes from the assessment of the vitamin D status in treatment-naïve SLE patients: hypovitaminosis D is prevalent in SLE patients who has still not started a therapy compared to healthy controls (38.6% *vs.* 4.8%). Treatment-naïve SLE with hypovitaminosis D has been found to be associated with a higher ANA titre and with high serum levels of pro-inflammatory cytokines IL-17 and IL-23 (16).

Cardiovascular disease (CVD) is one of the main causes of death in SLE patients, but the Framingham score often underestimates the risk for CVD in this population. A cross-sectional

controlled study revealed a correlation between serum high-sensitivity cardiac troponin T (HS-cTnT) and the presence of carotid plaques (assessed by ultrasound). High serum HS-cTnT levels are therefore associated with carotid plaques in SLE patients who are at an apparently low risk for CVD according to the Framingham score (17).

Among the new biomarkers, elevated levels of soluble CD40L (sCD40L) are involved in the atherotrombotic disease and are reported in SLE patients; Kim *et al*. found higher levels of sCD40L in SLE patients with positive aPL and arterial thrombosis, suggesting a possible relationship between platelet activation presumably by aPL and sCD40L contributing to the development of atherothrombotic disease (18).

As previously said, one of the most demanded use of biomarkers is their capability to predict disease activity. For example, a study showed how serum osteopontin (OPN) levels, an extracellular matrix protein with immunomodulating properties, are in average raised fourfold in SLE cases compared to controls ($p<0.0001$). Data indicate that OPN correlates with disease activity in recent-onset SLE, reflects global organ damage and associates with antiphospholipid syndrome (APS) (19).

Another article revealed how the recently identified T follicular regulatory (Tfr) cells, a subset that can migrate to the germinal center and inhibit T follicular helper (Tfh)-mediated B-cell activation, are reduced in peripheral blood from SLE patients. Moreover, low levels of Tfr cells and a high Tfh/Tfr ratio correlates with disease activity and also with elevated anti-dsDNA titre; which is corroborated by an increase in Tfr cells number and a decrease in the Tfh/Tfr ratio observed in successful treatments (20).

A Japanese study demonstrated that the levels of mucosal-associated invariant T (MAIT) cells, innate-like lymphocytes that rapidly exert effector functions upon activation without the need to undergo clonal expansion, are decreased in peripheral blood of patients with SLE. This reduction seems due to activation-induced cell death: MAIT cells in SLE are actually activated, and

the expression of the activation marker CD69 on these cells clearly reflects disease activity (21).

Serum and urine IFN-γ, chemokine (C-X-C motif) ligand 16 (CXCL16) and soluble urokinase-type plasminogen activator receptor (suPAR) levels in SLE patients have been found significantly higher than in healthy controls. Between these markers, suPAR had a stronger association with disease activity. The expression of these biomarkers in renal tissues was significantly higher in LN patients and was also associated with the severity of histopathological lesions (22).

A prospective longitudinal benchmark study revealed that IFN-γ-inducible protein-10 (IP-10) and sialic acid-binding Ig-like lectin 1 (SIGLEC1) could be considered as two excellent biomarkers for monitoring disease activity. Their serum levels significantly increase during flares (IP-10 p=0.017; SIGLEC1 p=0.008) and decrease during remissions (IP-10 p=0.04; SIGLEC1 p=0.04). This is an important finding because other traditional biomarkers do not have such a versatility in reflecting longitudinal changes in disease activity (23).

Biomarkers of specific organ involvement

Reliable urinary biomarkers could improve in a considerable way the management of LN: they would allow a better assessment of the kidney microenvironment than peripheral blood, giving that predictive accuracy that could make renal biopsy not so strictly necessary.

Using ELISA technique, it has been demonstrated that two urinary proteins, alpha-1-antichymotrypsin (ACT) and haptoglobin (HAP) are detected only in patients with active renal disease, while are absent in urine from SLE patients with inactive disease ($p<0.001$), correlating furthermore with SLEDAI ($p<0.001$). Another urinary protein, retinol binding protein (RBP), showed a slightly lower correlation, but even so it is considerable a reliable marker (24). Neutrophil gelatinase-associated lipocalin (NGAL) and monocyte chemoattractant protein-1 (MCP-1) serum and urinary levels are significantly higher in patients with SLE as compared to

healthy controls. In addition, urinary NGAL is markedly increased in SLE with LN than in SLE without renal involvement (25), while elevated urinary MCP-1 concentration is a marker of renal flare in LN, positively correlating with proteinuria and SLEDAI, and with the reduction of C3 and glomerular filtration rate (26).

Thanks to microarray technology it is possible to evaluate and subsequently dose (with qPCR) miRNA even in the urine: an American study analysed urinary miRNA from SLE patients with biopsy-proven LN (classes II-V), SLE without LN and healthy controls. They found that urinary miR-3201 and miR-1273e are down-regulated in LN patients (>3-fold, $p<0.0001$) and, on a histopathological point of view, are associated with endocapillary glomerular inflammation (27).

A British study deepened the role of non-contrast multi-modal renal MRI in LN comparing the results with urinary protein-creatinine ratio (uPCR) and estimated glomerular filtration rate (eGFR). The techniques used were arterial spin labelling (ASL), able to measure regional renal blood flow and perfusion, diffusion tensor imaging (DTI), useful for evaluating microstructural disruption, and T2*-weighted sequences, which reveal micro-haemorrhages. DTI provides two MRI biomarkers: apparent diffusion coefficient (ADC) is a measure of the diffusion path-length of tissue water molecules, and is increased when diffusion is relatively unimpeded as in edema or necrosis, while fractional anisotropy (FA) describes the dominate direction of diffusion, so that highly structured tissues, such as renal tubules, exhibit high anisotropy, while damaged or inflamed tissue becomes disorganised leading to lower FA. It was found no significant association between LN activity and ASL measurements, although there was a trend towards correlation between medullary flow and eGFR. DTI showed that medullary ADC associated significantly with eGFR (p=0.03) and there was a strong inverse correlation between cortical FA and uPCR ($p<0.01$), demonstrating the pathogenic role of microstructural disruptions. Eventually T2*

values correlated inversely with uPCR (*p*=0.013) (28).

There is a lack of biomarkers that are able to assess pulmonary involvement in SLE It has recently been demonstrated that serum levels of CC chemokine ligand 21 (CCL21) and of the previously cited IP-10 are significantly higher in SLE with lung involvement than in patients without pulmonary manifestations. More specifically, CCL21 correlates negatively with DLCO (sensitivity: 88.90%; specificity: 75.00%; *p*<0.01), whilst IP-10 with FVC and FEV1 (sensitivity: 66.67%, specificity: 100%; *p*<0.01) (29).

Evaluating the prevalence of anti-carbamylated proteins antibodies (anti-CarP), a recent biomarker already used for rheumatoid arthritis (RA), in SLE cases with joint involvement (arthralgia or arthritis), it turned out that almost 50% of the patients resulted positive for anti-CarP. This prevalence is similar to that identified in RA cases and is significantly higher as compared to SLE patients without joint involvement and healthy controls (30).

MRI is the imaging technique of choice for neuropsychiatric SLE (NPSLE), although up to 50% of cases have no apparent abnormalities. A recent study evaluated MRI findings in NPSLE applying DTI to assess white matter (WM) and gray matter (GM) damage. It turned out that NPSLE patients had a higher diffusivity and a significant reduction in GM and WM as compared to controls (SLE without NP involvement and healthy controls) in fronto-temporal regions, positively associating with SLEDAI, reduction of C3 and long-standing disease. Atrophy involving frontal and temporal GM or WM is therefore considerable a hallmark of NPSLE, correlating with severity, activity and time from disease onset. Interestingly antimalarial treatment correlated negatively with atrophy in frontal cortex and thalamus, leading to think that antimalarial therapy seems to give some brain-protective effects (31).

Clinical manifestations
Gender and ethnic factors
The diversity in the prevalence of the various SLE manifestations suggests that gender and ethnic factors play an important role in the expression and severity of the disease.

Leng *et al.* compared demographics, clinical manifestations, and laboratory data between patients with familial lupus (FL), family history of other rheumatic disorders (RD), and sporadic lupus (SL) from the Chinese lupus treatment and research group (CSTAR) registry; they found a lower rate of familial lupus than among other ethnicities, moreover, a family history of lupus did not significantly affect clinical phenotypes, except for higher frequency of discoid rash and anti-RNP in the FL group, and more anti-RNP positivity in the RD group (32).

In a recent article it was pointed out that in Caucasian SLE patients the age at diagnosis and the symptom onset are higher in men than in women (37 *vs.* 32 years) and the diagnostic delay is shorter in men. Male patients present more cardiovascular comorbidities, serositis, adenopathies, splenomegaly, renal involvement, convulsion, thrombosis, and lupus anticoagulant positivity than women. However, inflammatory rash, alopecia, arthritis and Raynaud's phenomenon are more common in women (33). The same results were obtained in a cohort of Canadian patients where the mean age at diagnosis was lower in women (42.3 *vs.* 48.9 years). Moreover, cutaneous manifestations were less frequent in older age groups while haematologic and renal manifestations were more common in young adults. The occurrence of musculoskeletal symptoms was similar between sexes, and renal manifestations were more common in males than females. For both sexes, lung involvement was the least common (34).

In a publication on Sudanese patients with a clear predominance of Arab ancestry, arthritis was the most common clinical manifestation, reported in 85.5% of patients. Constitutional symptoms such as fever, fatigue and weight loss were reported in 72.6%, while renal involvement in 66.1% of patients (33). A recent study of the Hakka population in southern China showed that arthritis was the main clinical manifestation (61.6%) in SLE patients, followed by nephritis and anaemia (36). Also in Spanish patients there was a predominance of joint manifestations (74.5%) at the first visit. Moreover, in this record of cases there was a higher rate of LN, haemolytic anaemia and lymphopenia (35). While all these data concern adult SLE patients, Torrente-Segarra *et al.* analysed the Spanish Society of Rheumatology Lupus Registry to establish differences between juvenile-onset SLE (484 patients) and adult-onset SLE (3.428 patients). In patients with juvenile-onset SLE, it was found a more frequent familiar history of SLE, a longer diagnosis delay and a significantly more severe clinical and immunological involvement than in adult-onset SLE (38).

Neurological involvement
Many different neuropsychiatric features are described in SLE patients regarding central nervous system (CNS) and peripheral nervous system (PNS), as well as psychiatric disorders.

PNS manifestations, even if rare, are a major cause of morbidity. Toledano *et al.* recently noted that the most frequent PNS manifestation in SLE patients was polyneuropathy, followed by non-compression mononeuropathy, cranial neuropathy, myasthenia gravis and Guillain-Barré syndrome (39). Moreover, it was observed that myelitis appears early during the course of the disease and causes a significant increase in the cumulative damage compared to other acute non-neuropsychiatric manifestations (40).

SLE is an independent positive predictor for epilepsy, and this evidence was confirmed also adjusting for multiple confounding factors (age, sex, and socioeconomic status). The percentage of epilepsy was higher (4.03% *vs.* 0.87%) among SLE patients than in controls (41).

In a Swedish study the relative risk of ischaemic stroke in SLE was more than doubled as compared to general population. Furthermore, the highest risk was for females and adults <50 years old. The most relevant relative risk was observed within the first year after SLE diagnosis and remained relatively constant up to 11 years of follow-up. Again,

mean age at stroke was younger in SLE compared to healthy controls (68.4 *vs.* 73.3) (42).

Cohen *et al.* analysed brain histopathology from 16 patients with NPSLE, 18 SLE patients without neuropsychiatric involvement and 24 patients who died of acute cardiac events served as controls. This study demonstrated that NP-SLE patients significantly present more micro-infarction, macro-infarction, vasculitis and microthrombi than those without neuropsychiatric involvement. These and other neuropathological abnormalities were absent in healthy controls. Furthermore, deposits of complement components C1q, C4d and C5b-9 were found significantly more often in SLE cerebral vessels (both NPSLE and non-NPSLE) than in controls (43).

Depression is quite common in SLE. Park *et al.* performed a multivariable logistic regression analysis to evaluate risk factors for depression in 505 Korean SLE patients. The authors pointed out that the factors associated with depression are current smoking status, anticardiolipin-positivity and a SLICC damage index score >1. On the other hand, high-level of education and a high income were negatively associated with depression (44).

Cardiovascular and pulmonary involvement
Cardiac involvement in SLE may include the pericardium, myocardium, valvular tissue, and coronary arteries. Lupus myocarditis is a severe condition, it can be the onset manifestation of SLE or it can occur during the course of the disease. According to a recent paper, the lack of specific treatment may favour the development of myocarditis in SLE patients. Fortunately, the long-term prognosis of this manifestation is generally positive (45).

Using logistic regression, Mok *et al.* analysed 577 SLE patients to study the effect of metabolic syndrome on organ damage and on mortality rate. It was concluded that the presence of metabolic syndrome significantly increases the risk of vascular mortality (OR 28.3), new vascular events (OR 3.38) and new organ damage in renal (OR 5.48) and endocrine system (OR 38.0) (46).

As far as lung involvement is concerned, pleuro-pulmonary manifestations were present in approximately one third from a cohort of 1480 Latin American SLE patients; the most frequent finding was pleuritis which occurred in 24.0% of the cases (47).

Renal involvement
It was recently conducted a retrospective cohort study over 20 years that included 249 SLE patients with renal involvement (proved by renal biopsy). In these patients symptoms of renal flare included hypertension in 40%, nephrotic syndrome in 30%, and renal failure in 69.4% of the cases. Flare predictors were age <30 years and diffuse proliferative LN. A significant association with lymphopenia and discontinuation of immunosuppressive therapy was also identified. The occurrence of flares was not significantly associated with immunological markers such as antibodies against dsDNA or complement levels (48).

Haematological involvement
Haematological involvement can already be found at the time of diagnosis or it may occur afterwards, as a part of disease clinical spectrum or induced by medications. The most common haematological disorders are lymphopenia and anaemia as shown in a cohort of 221 patients studied by Teke *et al.* Regarding cytopenia, it was already present in 83.3% of the cases at the time of diagnosis; besides cytopenia was disease-related in 83.4% of the patients while in 16.6% it was medication-related. In cytopenic SLE patients, renal involvement and APS were more frequent as compared to non-cytopenic SLE cases (49).

SLE was found to be independently associated with a higher proportions of malignancies, particularly the haematologic ones. The most frequent were non-Hodgkin lymphoma followed by Hodgkin lymphoma and multiple myeloma (50).

Ocular involvement
As recently showed by Gao *et al.* the prevalence of retinal vasculopathy was approximately 0.66% in SLE patients

and this manifestation was found to be significantly associated with neuropsychiatric lesions and haematological disturbances. Ocular manifestations included decrease of visual acuity, visual field loss and diplopia. Furthermore, SLE patients with retinal vasculopathy had significantly higher SLE disease activity index scores than controls. The presence of anti-SSA antibodies was instead a protective factor for these manifestations (51).

Skin involvement
Raynaud's phenomenon is frequently reported in SLE patients and morphological changes in nailfold capillaroscopy are very common even if there is not a specific pattern. It was recently reported that in patients with active skin involvement, an abnormal capillary distribution could be detected more frequently than in cases without active skin manifestations. Moreover, elongated capillary loops were seen more often in patients with LN than in patients without renal involvement (52).

Comorbidities
As knowledge about the pathogenic mechanisms of SLE has been increasing, several immunosuppressive agents have become routinely used in clinical care and infections have become one of the most important causes of mortality. The increased risk of infections in this population is probably due to the combined effect of immune system dysregulation and immunosuppressive therapies, especially in cases of high disease activity and LN. A retrospective cohort study including 189 patients who had biopsy-proven LN, analysed rates of hospitalisations for infections between 2000 and 2009 and observed that 104 of them (60.3%) had at least one hospitalisation for infection at 11 months from diagnosis. LN relapse was a factor associated with hospitalisation for infection (53).

Chen *et al.* examined the adverse events correlated to longitudinal glucocorticoid (GC) use in 11288 Chinese SLE patients and found that higher doses of GC were associated with increased risk of bacterial infections along with other non-infectious complications

(54). Feldman *et al*. compared infection rates among SLE patients newly initiating immunosuppressive therapy with mycophenolate mofetil (MMF), azathioprine (AZA) or cyclophosphamide (CYC) up to 6 and 12 months after drug initiation. They studied 1350 propensity score-matched pairs of MMF and AZA initiators and 674 propensity score-matched pairs of MMF and CYC initiators and found an increased infectious risk in all groups but no significant differences between the three groups in terms of serious infections and mortality rates (55).

Some recent papers focused on hospital-acquired infections (HAI) in SLE. In a case-control study involving 3956 Chinese SLE patients with HAI it was found that respiratory tract was the most commonly involved (58.8%), followed by bloodstream infections (10.9%). Most episodes were bacteria-associated (50.0%), coming before viral (34.8%) and fungal infections (15.2%). SLE-DAI score, LN, high dose of GC and treatment with CYC were risk factors for HAI (56).

SLE patients also display a slightly higher overall risk of malignancy. This increased risk is probably due to immune and genetic pathways underlying the pathogenesis but also to immunosuppressive therapies. A cross-sectional population-based study including 5018 SLE patients and 25090 controls demonstrated that SLE diagnosis was independently associated with higher proportions of malignancies, particularly haematologic conditions, but even cervix uterine cancer and genital organ malignancies (57). In a large retrospective case-control study of SLE patients, it was found an association between a higher cumulative CYC dose and cancer risk. The most frequent cancer types were the breast (16.9%), haematological (11.7%), colorectal (11.0%), lung (10.6%) and hepatobiliary (10.4%) ones (58). A significant risk of cervical cancer in SLE patients receiving immunosuppressive drugs was also confirmed by two recent large cohort studies, highlighting that the association was higher in these patients if compared to those treated with antimalarials (59-60). An increased risk of diffuse large B cell lymphoma (DLBCL) in SLE patients has been demonstrated too. Bernatsky *et al*. investigated 28 SLE-related SNPs and found that the most associated with DLBCL were the CD40 SLE risk allele rs4810485 on chromosome 20q13 and the HLA SLE risk allele rs1270942 on chromosome 6p21.33. Given that CYC exposure in SLE is also associated with DLBCL risk, in future these genetic risk factors may play an important role in risk stratification and decision-making when CYC treatment is considered for severe forms of SLE (61).

Osteopenia and osteoporosis are further complications in SLE deriving from multiple possible etiologies: systemic inflammation, GC use (54) and estrogen deficiency. However, the exact mechanism underlying osteopenia and osteoporosis in SLE patients newly diagnosed remains unknown. In a recent study Guo *et al*. found that newly diagnosed SLE patients showed a significant reduction of osteocalcin, a marker of bone formation, while serum β-crosslaps level (marker of bone resorption) was markedly elevated. SLE disease activity negatively associated with osteocalcin, while positively correlated with β-crosslaps (62). The analysis of potential risk factors for vertebral fractures (VF) in SLE was conducted in 110 SLE patients and it was found that incident VF were significantly associated with baseline bone mass density (BMD) at the total hip and with longer disease duration (63).

In an extensive analysis on 4,278 SLE patients and 16,443 age and sex-matched controls, in contrast with several previous report showing an association between SLE and low vitamin D, Watad *et al*. found that SLE patients had slightly higher levels of vitamin D while SLE were twice as likely to experience episodes of hypocalcaemia in comparison to controls; this in a novel observation that requires further confirmations (64).

In a meta-analysis of 62 articles, prevalence and risk factors for avascular necrosis (AVN) were investigated; the authors reported a prevalence of symptomatic AVN of 9% and 29% for asymptomatic AVN with the femoral head being the most affected location. Disease activity, therapy with glucocorticoids and anti-cardiolipin antibodies were found significantly associated with AVN (65).

Cardiovascular risk
SLE is associated with increased cardiovascular (CV) risk and with CV events (CVE) occurring at a significantly younger age than controls. The Toronto Risk Factor Study recruited 250 female SLE patients and 250 controls and found that, after 7 years of follow-up, SLE patients had a significantly higher rate of clinical coronary artery disease (CAD). SLE itself, older age at study entry and triglycerides >2.8 mmol/L were predictive of CAD and after 15 years of follow-up it was found that SLE diagnosis, age at study entry, number of traditional risk factors, VLDL, homocysteine ≥ 15 μmol/L, and high levels of C-reactive protein were predictors for CVE in all participants. While disease-related factors seem to predominate CV risk in SLE during the early stages, traditional factors play a more significant role later in the disease course (66). CVE predisposition in SLE patients is even due to the acceleration in the atherosclerotic process. Tektonidou *et al*. performed carotid and femoral artery ultrasonography in 115 SLE patients demonstrating that the relative risk of subclinical atherosclerosis in SLE was comparable to that found in RA and diabetes (67). Furthermore, another study found that excessive carotid plaques were essentially peculiar to the SLE subgroup with LN, with an age-matched double-fold incidence compared to non-LN SLE patients and healthy controls (68). Stroke risk in SLE patients is almost doubled compared to the general population, evidence confirmed by a study including 3390 people with SLE and 16730 controls. The highest relative risks were observed within the first year after SLE diagnosis. Furthermore, a higher proportion of SLE individuals with stroke were female (79% *vs*. 68%) and younger than the general population (69).

A Spanish study demonstrated that insulin resistance (IR) plays a role in the increased cardiovascular risk of SLE patients; in 87 non-diabetic SLE C-

peptide levels were significantly higher than in controls, moreover, not only traditional cardiovascular risk factors and glucocorticoids resulted associated with IR, but also SLE-specific factors such as organ damage (70).

Therapy

Belimumab and novel anti-BAFF agents

In 2017 several published studies concerning the novelties in lupus therapy refer primarily to belimumab and novel anti-BAFF agents.

Belimumab is a fully human monoclonal antibody (mAb) that binds to B cell activating factor (BAFF, also known as B lymphocyte stimulator or BlyS). Licensed in 2011, it is the first biologic drug approved for SLE treatment. A phase III trial including 839 SLE patients investigated the efficacy and safety of subcutaneous belimumab at the dose of 200 mg plus standard of care (SoC). It demonstrated similar efficacy, safety and tolerability as intravenous belimumab (71). Consequently in 2017, FDA approved subcutaneous belimumab, administered weekly at a dose of 200 mg, for the treatment of active autoantibody positive SLE patients receiving standard therapy.

Seven years after its first approval, it is still unclear which patient subgroups are expected to best benefit from Belimumab. Real life studies tried to better clarify this concept.

In 2017 different real life observational studies confirmed that belimumab, in addition to standard therapy, is a safe and effective treatment for active lupus patients. They also confirmed that musculoskeletal and skin manifestations appear to benefit the most of Belimumab, moreover patients with higher disease activity, anti-DNA antibodies and hypocomplementaemia or with a higher steroid dose tend to show a better response (72-73).

Interestingly, a Swedish group found that smoking and established organ damage predicted reduced efficacy of belimumab. They further found that high baseline BLyS levels also predicted favourable treatment outcomes. Additional questions on long-term outcomes remain to be established (74).

Regarding vaccinations, a Sweden paper showed that belimumab, given in addition to traditional disease-modifying anti-rheumatic drugs (DMARD) or prednisolone, does not further impair antibody response to 13-valent conjugated pneumococcal vaccine (75).

Another study which compared 23-valent pneumococcal vaccine responses between pre-belimumab and concurrent-belimumab patients, showed that 80% of both groups responded to ≥12 serotypes, and approximately two-thirds responded to ≥16 serotypes, showing no differences between the pre-belimumab and concurrent-Belimumab cohorts (76).

In conclusion, data from recent observational studies confirm belimumab long-term safety and efficacy and its capability to achieve a positive long-term impact on damage accrual and quality of life.

The identification of BAFF's key role as a B cell survival, activation, and differentiation cytokine involved in SLE pathogenesis has led to the development of novel anti-BAFF agents with promising clinical results in SLE.

Among novel anti-BAFF mAbs, there is blisibimod, which is building on the success of belimumab by targeting both soluble and membrane-bound BAFF. Early-phase clinical trials of blisibimod have proven its safety and tolerability and have provided a hint of efficacy, specifically in a subpopulation of SLE patients with higher disease activity (77).

Blisibimod was tested in SLE in phase I and II trials where it showed safety and tolerability (78).

In a recent phase III trial, although the primary end point was not met, blisibimod was associated with successful steroid reduction, decreased proteinuria and biomarker responses (79).

Currently, CHABLIS 7.5 (NCT025-14967), a phase III randomised double-blind placebo-controlled trial, is evaluating the efficacy and safety of Blisibimod in SLE participants with or without LN. This trial is actively enrolling participants since June 2016 with the goal of completion in December 2018. The advantage of blisibimod, compared to its competitors, lies in its

higher avidity for BAFF, but a possible drawback may come from its immunogenic potential and the anticipated loss of efficacy over time.

Another new anti-BAFF mAb is atacicept, a fusion protein between the BAFF receptor, TACI, and the Fc portion of human IgG1. Atacicept targets soluble and membrane-bound forms of both BAFF and APRIL. APRIL is a proliferation inducing ligand, member of the TNF ligand super-family, that shares substantial homology with BAFF and binds to two of the three BAFF receptors (BCMA and TACI). As BAFF, APRIL plays a particularly crucial role in early B cell development. The rationale for targeting these pathways is provided by the observation that both BAFF and APRIL levels are increased in SLE patients. Although higher risk of serious infections and unsafe drop in serum IgG were observed in previous phase II/III trials (80-81), atacicept may still offers good perspectives for SLE. In fact, the *post hoc* analysis of Phase II/III APRIL-SLE study demonstrated a dose-response relationship between Atacicept concentrations and flares reduction: flare rates were reduced with Atacicept 150 mg (82).

Linking to the previous work, also the phase IIb ADDRESS II study observed reductions in the incidence of severe flares with atacicept *versus* placebo (83). In conclusion BlyS targeting (not APRIL) emerges as a safe alternative to manage moderately active lupus with modest overall effects. Patients with active musculoskeletal and skin disease or who depend on GC for disease control remain the best candidates for these biologics (84).

Rituximab and new biologic therapies against B cells.

BAFF levels have been consistently described as increased after B-cell depletion via anti-CD20 approaches and it has been described as higher in SLE patients experiencing a relapse after rituximab (RTX) administration when compared to patients who maintain disease remission. Sequential treatment with RTX followed by belimumab could represent a promising strategy

for SLE and LN by interfering with rebound increases in BAFF levels due to B-cell depletion, thus favouring the sustained depletion of auto-reactive B cells (85).

Regarding RTX in monotherapy, some papers were published in 2017. A recent retrospective study showed the efficacy and tolerance of RTX as monotherapy in induction treatment of pure membranous LN (86) while another study reported long-term (up to 7 years) results and data of RTX use in newly diagnosed SLE (87). It was concluded that early treatment of SLE patients with B-cell depletion is safe, effective and enables a reduction in steroid use.

Another study about the long-term effects on B cell in SLE patients treated with RTX showed that hypogammaglobulinaemia after RTX was largely restricted to the IgM class and was mainly associated with lower baseline IgM levels and with sequential MMF therapy (88).

An English prospective observational study was conducted in patients with moderate-to-severe SLE who were treated with RTX. The study assessed factors associated with primary and secondary non-response to RTX and evaluated secondary non depletion non response (2NDNR) management. It concluded that RTX treatment can be guided by B-cell monitoring with the aim of achieving complete depletion. About 12% of SLE patients with lost depletion on repeated RTX cycles regardless of prior response met 2NDNR criteria and were found positive for anti-RTX antibodies (89). Concomitant oral immunosuppressant may help to prevent this. If 2NDNR occurs, switching to humanised anti-CD20 mAbs restores depletion and response. Therefore, in SLE alternative anti-CD20 antibodies may be more consistently effective; several ongoing trials are addressing these issues.

The central role of B cells in SLE pathology led to the advent of new biologic therapies targeting B cells. One of those is Epratuzumab, a humanised mAb directed against CD22 on B cells. However, data from EMBODY 1 (NCT01262365) and EMBODY 2 (NCT01261793), two phase III randomised double-blind placebo-controlled trials regarding epratuzumab in patients with moderate-to-severe active SLE, did not confirm its clinical efficacy so the drug has been now abandoned (90).

Among new B-cells depleting agents there is bortezomib, a haematologic drug approved for multiple myeloma and lymphoma. It is a proteasome inhibitor that can downregulate plasma cells function, reducing antibody secretion. Zhang *et al.* have reported 5 cases of SLE patients with refractory LN treated with bortezomib combined with GC, with encouraging results on renal function, proteinuria, immunological parameters and mild adverse events (91).

In conclusion the only biologic drug currently approved for SLE is Belimumab, an anti-BLyS agent with modest effect on disease activity. Other B-cell targeted therapies failed to show an effect in large phase III trials despite early promising results (84).

Inhibitors of IFN-I

It is known that SLE is a prototypical IFN-I-mediated autoimmune disease. Increased levels of serum IFN-I were detected in SLE patients more than 30 years ago and were associated with disease activity (92).

Most SLE patients, in contrast to healthy individuals, show a sustained activation of the IFN-I system which reflects an overexpression of type I IFN-regulated genes or an IFN-signature. The persistent production of IFN-I in SLE patients is due to the continuous stimulation of pDCs by endogenous nucleic acids. IFN-I stimulates both the innate and adaptive immune systems, thus playing an important role in the autoimmune disease process. Some of the standard therapies for SLE, like high doses of GC and hydroxychloroquine (HCQ), downregulate IFN-signature. In particular, HCQ seems to exert its effect on IFN-I by blocking TLR7 and TLR9 activation (93).

However, given the central role of the IFN-I system in SLE pathogenesis, IFN-targeted therapies still represent an active area of investigation.

Inhibitors of type I IFN-system have been recently developed. Among these, neutralising IFN-I mAbs have shown encouraging results. Sifalimumab, a fully human IgG1κ mAb that binds to and neutralises most IFN-α subtypes, demonstrated to be effective in patients with active moderate-to-severe SLE, refractory to standard of care, in a phase IIb randomised double-blind placebo-controlled study (94).

Sifalimumab treatment was associated with improvement in both general SLE composite endpoints and individual organ system endpoints. Exploratory analyses suggested that patients with high IFN gene signature expression responded better than those with a low one. In any case, due to the small number of patients with a low IFN gene signature, a meaningful statistical comparison between the two groups was not possible (95).

Given the multiple forms of type I IFN, a more complete inhibition IFN-I system may be obtained by targeting the shared IFNAR1 receptor.

Anifrolumab is a mAb directed against IFNAR1. It has been evaluated in adults with moderate-to-severe SLE in a phase IIb randomised double-blind placebo-controlled study whom results were published last year. 305 patients were randomised to receive intravenous anifrolumab (300 mg or 1000 mg) or placebo, in addition to standard therapy, every 4 weeks for 48 weeks. Randomisation was stratified by SLEDAI score (<10 or ≥10), oral GC dosage (<10 or ≥10 mg/day) and type I IFN gene signature test status (high or low) based on a 4-gene expression assay. Anifrolumab met its primary endpoint of a reduction in global disease activity score in SLE patients. Moreover, the drug demonstrated its superiority compared with placebo across other multiple clinical endpoints. For all outcomes, the treatment effects were most pronounced in patients with a high IFN-signature at baseline. Concerning the drug's safety profile, a dosage-related increase was observed in the occurrence of upper respiratory infections and reactivation of herpes zoster. Thus, a more favourable risk/benefit profile emerged for the 300 mg dosage (96).

The risk/benefit assessment emerged with anifrolumab was greater than that

with Sifalimumab in a similar population. This is probably due to the different targets of these mAbs: the shared IFNAR1 receptor and IFN-α, respectively.

Traditional immunosuppressive drugs
Nowadays standard treatment for active LN is MMF or CYC combined with high-dose steroids. However, some patients do not respond to standard treatment. There is growing evidence that calcineurin inhibitors, including cyclosporine A (CsA) and tacrolimus (TAC), are promising agents for the treatment of refractory LN.
A retrospective study demonstrated that low-dose CsA could induce renal remission and ameliorate SLE disease activity in patients with resistant proliferative LN, representing a safe drug for the treatment of these patients (97).
Furthermore, some papers published in 2017 assessed the efficacy of calcineurin inhibitors in combination with traditional immunosuppressants, such as CYC or MMF, in LN treatment. In a prospective single-arm open label pilot study recruiting 15 patients with active LN, all participants were treated with a starting dose of 0.61 mg/kg/day prednisolone for 2 weeks then tapered to a maintenance dose, intravenous CYC (500 mg biweekly for 3 months) and TAC (3.0 mg/day). TAC was then continued as maintenance therapy. Those patients were compared to 18 controls conventionally treated with CYC and prednisolone. At 6 months, 12 of 15 patients of the study achieved complete remission, significantly more than controls (7 of 18 patients) (98).
Another prospective multicentric randomised controlled trial compared TAC and MMF for induction and maintenance therapy in LN. Adult patients with active nephritis received prednisolone (0.7–1.0 mg/kg/day for 4 weeks of run-in period and then tapered) and were randomly assigned to receive TAC (0.1 mg/kg/day) or MMF (1.5–2 g/day) as induction therapy for six months. The study concluded that TAC was comparable with MMF during induction but MMF was more effective on disease activity for active LN classes III and IV at 12 months (99).

Other
In the last decades, our understanding of SLE pathogenesis has increased. Reflecting the increasing knowledge of the different immune mechanisms that contribute to lupus pathogenesis, a variety of other therapeutic targets have been recently evaluated. For example, the strategy of blocking the IL-6 pathway, known to be successful in RA, has been tested in SLE patients too. Tocilizumab and sirukumab gave disappointing results. The preliminary results of a phase II dose-ranging randomised controlled trial of another anti-IL-6 mAb (PF-04236921) did not show significant differences from placebo for the primary efficacy endpoint in SLE patients (100). Some biologic drugs already used in other rheumatic diseases were also evaluated in SLE. For instance, last year some anecdotal cases about successful use of ustekinumab in severe, refractory, discoid lupus lesions were reported (101).
Leng *et al*. reported the results of a 10-year follow up of a group of 24 Chinese patients with severe SLE after high-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation (APBSCT). The 10-year overall survival rate and 10-year remission survival rate were both 86.0%, so the authors suggest that this therapeutic strategy may be considered to improve the outcome of severe SLE patients (102).
In contrast, Deng *et al*. found no apparent additional effect of human umbilical cord-derived mesenchymal stem cells over standard immunosuppression for LN treatment (103).
In conclusion, recent progresses in the understanding of the mechanisms involved in SLE have led to the development of novel therapies for this disease. Nevertheless, the heterogeneous and persistent nature of SLE manifestations remains a burden for many patients, and agents need to be developed to address the substantial unmet medical needs for this disease (104).

Quality of life and patient-reported outcomes
SLE is a complex and unpredictable chronic disease which significantly impacts on patients' daily living. Despite the advances in overall SLE prognosis, patients' quality of life has not improved.
EULAR recommendations for monitoring SLE patients establish that Health-Related Quality of Life (HRQoL) has to be evaluated at every visit in routine clinical practice, as an independent outcome measure (105). HRQoL is a multidimensional concept of a patient's well-being which takes physical, mental, emotional and social functioning into consideration. It refers to the impact that a disease and its treatment has on individual's life.
HRQoL is generally poorer in SLE patients than in general population.
In a recent survey performed among the Lupus UK members, almost three-quarters of individuals had problems limiting their ability to carry out their usual daily activities, and only 15% of them worked full time. Moreover, many patients declared that they require day-to-day support, not only from health care professionals, but also from the partner, family members and friends. Thus, SLE determines significant limitations in daily living, work loss and a need for continuous support from others (106).
Similarly, the considerable burden of SLE for patients and their carers has emerged from an online survey conducted in the UK. The survey revealed that fatigue was the most debilitating symptom experienced by the majority of SLE patients. SLE showed a considerable impact on patients' physical, social and financial status. In particular, most patients (89%) reported reduced ability to socialise; 76% of them had changed employment and, of these, 52% stopped working completely.
SLE also showed a heavy impact on carers, both for their financial status and their social activities (107).
SLE seems to have a greater impact on patients' QoL even when compared with other rheumatic diseases. For example, in comparison with RA, it seems that RA patients achieve a better QoL than SLE patients at sustained remission (108).
In a recent study by Chaigne *et al*., HRQoL in patients with SLE and RA, matched by age, sex and disease du-

ration, was evaluated by the Medical Outcomes Study Short Form 36 (SF-36). SLE Patients had lower Mental Component Summary (MCS) scores, whereas RA patients had lower Physical Component Summary (PCS) scores and these differences remained even after adjustment for patient characteristics, treatment and disease activity, and even over 1 year of follow up. So, these results suggest that fundamental dissimilarities exist between SLE and RA in their impact on QoL (109).

Many factors influence HRQoL in SLE patients and it would be important to understand them for an effective management of the disease. First of all, we have to consider symptoms related to disease activity, disease severity and/or organ damage.

In a recent cross-sectional study of patients included in the Swiss SLE Cohort Study between April 2007 and June 2014, it was in fact demonstrated that an increase in SELENA-SLEDAI or in Physician Global Assessment was negatively correlated with PCS and/or MCS scores of the SF-36. In particular, the authors found that active LN and musculoskeletal involvement were associated with physical limitations and emotional problems, increased bodily pain and poor social functioning, while the serological activity (low complement and/or presence of anti-dsDNA antibodies) was associated with increased fatigue and reduced mental health (110).

Taking this into account, a "treat-to-target" strategy in SLE management, with the aim of achieving a remission or a low disease activity state and avoiding damage accrual in the long-term, appears of great importance in order to improve patients' HRQoL. Last year Golder *et al*. prospectively evaluated HRQoL, by means of the SF-36, in a large cohort of SLE patients and found that the attainment of a low disease activity state correlated with better PCS and MCS scores and with better scores in multiple individual SF-36 domains (111).

In a large cohort of Chinese SLE patients, it was demonstrated that durable remission (≥5 years) was significantly associated with less damage accrual and better QoL. It is interesting to note

that in this study HRQoL was evaluated both with a generic measure, the SF-36, and with a disease-specific measure, the LupusPRO, and that the condition of stable remission correlated with higher scores in both these HRQoL evaluation tools (112).

It is easy to imagine that a major organ involvement, in SLE patients, can affect HRQoL.

A recent study investigated QoL in LN patients, using the LupusPRO questionnaire. LN cases had poor QoL and patients with active LN had worse HRQoL and non-HRQoL as compared to patients without active LN. In particular, both active and past LN cases showed significantly worse HRQoL in medication and procreation domains of LupusPRO (113).

Neuropsychiatric involvement, another severe SLE manifestation, also seems to impact on QoL, as demonstrated in a recent paper where NPSLE patients had a significantly reduced QoL, compared to general population and patients with other chronic diseases (114).

However, SLE patients often present many disease manifestations that, even if not organ- or life-threatening, may equally have a significant impact on their QoL.

For instance, two recent Italian studies pointed out that musculoskeletal involvement importantly influences patients' daily living. Piga *et al*. showed that active arthritis, Jaccoud's deformities and also fibromyalgia are associated with worse QoL (measured by means of SF-36v2 and FACITv4 fatigue scale). Moreover, it was found that fragility fractures, deformities and active arthritis negatively affect disability perception measured by the HAQ (115). Similarly, Tani *et al*. investigated the impact of joint involvement in a cohort of 50 consecutive SLE patients and found a significant correlation between the presence of arthritis (established by clinical and ultrasound evaluations) and VAS score for pain, patient's perception of disease activity and Global Health (116).

Despite these evidences, the literature data on the correlation between disease activity/severity and patients' quality of life are slightly conflicting. It is in

fact well known that patients with inactive SLE still have a decreased HRQoL. Therefore, other factors able to influence QoL should be considered such as demographic and socioeconomic conditions, fatigue, sleep disturbances, and also depression, cognitive impairment and executive dysfunction (117).

Fatigue is one of the most frequent symptoms reported by patients. Recently, factors influencing fatigue were studied in a cohort of 99 Turkish SLE patients compared to healthy controls. The level of fatigue, assessed by the multidimensional assessment of fatigue (MAF) scale, was higher in patients compared to controls and it was independent from disease activity. In contrast, fatigue resulted positively correlated with anxiety and depression and negatively affected quality of life, measured by the SF-36 (118).

A poor sleep quality may also have a correlation with fatigue, emotional discomfort and a poor HRQoL in women with SLE (119).

Social relationships have a great influence on patients' QoL. A recent longitudinal study showed that a denying or uninformed support from parents and friends produce a negative impact, indicating that HR-QoL is compromised when patients feel that their emotional needs are unrecognised. On the contrary, the study highlighted that HRQoL was positively influenced by the patients' perception of a greater "self-efficacy" in the management of their own disease (120).

For the treating physician, HRQoL remains a difficult domain to evaluate in clinical practice because it depends on many factors and because there are no efficient tools that could help clinicians to really understand the disease burden on patients' daily living.

When evaluating the disease, patients and physicians often have discordant concerns, focusing on different aspects of the disease itself.

There is a very interesting cross-sectional questionnaire study conducted at a tertiary disease-specific outpatient clinic in Melbourne, Australia. Patients and physicians were asked to complete a survey which included questions concerning QoL issues and questions

on disease activity and damage (based on the SLEDAI-2K and the SLICC-DI, respectively). In response to each item, participants were asked to rate their degree of concern on a standard five-point Likert scale. Physicians were also asked if they routinely investigated some particular aspects of the disease with their patients, while patients were asked if they had experienced each SLE manifestation. It emerged a significant discordance between patients and their physicians regarding their level of concern on a range of SLE-related issues. Patients' major concerns were related to aspects of HRQoL, such as fatigue and functional measures, while physicians mainly focused on organ manifestations. Importantly, the three highest ranked patients' concerns, all of which related to function, were not reported as routinely assessed by the majority of physicians (121).

It is clear that exists a gap communication between patients and care givers and it has to be overcome. The quality of communication with doctors is linked to improved health outcomes, in particular relatively to HRQoL, through increased patient participation in the management of the disease and trust in the physician. Moreover, the quality of patient-physician interaction may greatly influence patients' adherence to therapy.

In order to engage patients in their care process and improve clinicians' understanding of the impact of the disease, Patient Reported Outcome (PRO) measures are becoming increasingly important in the management of chronic diseases, like SLE.

PROs are health status evaluations directly reported by the patient without the need of interpretation by a physician and they are supposed to give complementary information to those captured by medical evaluation, based on clinical manifestations and laboratory aspects.

PRO measures for a self-reported assessment of disease activity have been developed in SLE.

The Systemic Lupus Activity Questionnaire (SLAQ) is based on the same items and scoring system as SLAM but excludes laboratory items. The SLAQ is completed by the patient that so can give an assessment of subjective disease activity. It was developed as a tool to screen for lupus activity and flares in large groups of SLE patients who are followed as outpatients. The SLAQ has been widely used in the last decades. Last year, Pettersson *et al.* compared patients' assessments of SLE disease activity, obtained with the Swedish version of the SLAQ, with physicians' assessments, using the SLAM and the SLEDAI-2K. The Swedish version of the SLAQ appeared as a reliable and valid tool, in fact the authors reported moderate to good correlations between patients' and physicians' assessments of disease activity, in most of the scores included in the SLAQ. A lower grade of correlation resulted for newly diagnosed SLE patients (<1 year) (122).

It seems increasingly evident that the integration of PROs with the classical physician evaluation may provide a more complete image of disease activity with a potential disease-modifying effect. In a recent randomised controlled crossover study, electronic PRO measures (e-PROMs) were used for remote monitoring of early SLE patients. The use of e-PROMs facilitated close monitoring of disease activity. In fact, SLEDAI score was significantly lower in patients who completed online e-PROMS, in comparison to the control group. Moreover, adherence to therapy was significantly (*p*<0.1) higher in the e-PROMs group (123).

The use of PROs is even more important for the assessment of HRQoL in SLE patients.

Several HRQoL measures have been designed and evaluated in SLE cases. Some are generic questionnaires, developed for a quality of life evaluation in any disease state, while others are disease-specific measures, developed exclusively for SLE. Generic measures allow comparison with other conditions, while SLE-specific measures can capture peculiar dimensions of HRQoL affected in SLE.

Among generic HRQoL measures, the SF-36 is the most widely used and it has been validated across different chronic diseases. It was also recommended by Outcome Measures in Rheumatology (OMERACT) IV for assessment in randomised controlled trials (RCTs) and longitudinal observational studies in SLE.

It is still not so clear whether the SF-36 is sufficiently sensitive to change with the fluctuations of QoL in SLE patients. According to a recent prospective Japanese study, the SF-36 demonstrated an acceptable reliability among Japanese patients with SLE. HRQoL measured by the SF-36 was reduced in Japanese SLE patients compared to Japanese general population and HRQoL resulted associated with disease damage, rather than disease activity (124).

The Patient-Reported Outcomes Measurement Information System (PROMIS) has recently been developed in US. It is conceived for a wide range of conditions and it wants to provide a set of publicly available, efficient and flexible measurements of PROs, including HRQoL. Last year, some studies pointed out that PROMIS may be a promising tool for measuring HRQoL in SLE patients too (125).

SLE-specific questionnaires to assess HRQoL have been developed since the early 2000s. The first one was the SLE-specific Quality of Life questionnaire (SLEQoL), followed by Lupus Quality of Life (LupusQoL) and SLE Quality of Life Questionnaire (L-QoL). Among these tools, the most widely validated and used is the LupusQoL, which has been validated in different populations. Responsiveness of this questionnaire has to be further elucidated. Recently, the sensitivity to changes of LupusQoL and SF-36, in a cohort of SLE patients with moderately to severely active disease, has been compared. Both the SF-36 and LupusQoL resulted sensitive to changes, reflecting both improvement and worsening. Importantly, the LupusQoL SLE-specific domains (planning, burden to others, body image and intimate relationships) were largely responsive to changes (126).

In 2012 Jolly *et al.* developed and validated a new specific tool, called LupusPRO, which showed good measurement properties. It was developed from feedback by US patients and, in the past years, its English and French versions were also validated among

SLE patients in Canada. Last year the Japanese version of LupusPRO was validated too (127). Besides, for the purpose of clinical trials, a new version of LupusPRO (1.8) was developed. In this version, the domain Pain-Vitality was separated into distinct Pain, Vitality and Sleep domains. This new LupusPRO v. 1.8 was validated in a cohort of consecutive SLE patients and demonstrated acceptable reliability and validity, suggesting that the use of LupusPRO as an outcome measure in clinical trials would facilitate responsiveness assessment (128).

In 2014 a short form instrument from the LupusPRO, the Lupus Impact Tracker (LIT), was derived. It is a 10-items questionnaire that provides a summary score that captures the overall impact of lupus on HRQoL. LIT was widely validated last year. In particular, the cross-cultural validity of LIT was evaluated in five European countries (France, Germany, Italy, Spain and Sweden). The results showed its reliability and cultural invariability across countries and it also appeared feasible thanks to its brevity (129). Finally, LIT was also validated in a Southeastern US cohort of SLE patients, with a large number of African American cases, and in an Australian cohort (130-131).

LIT responsiveness to changes in disease activity, using the SLE responder index (SRI) was evaluated in an observational, longitudinal, multicentre study conducted across the USA and Canada. LIT resulted moderately responsive to SRI in SLE patients. Inclusion of this tool in clinical care and clinical trials may provide further insights into its responsiveness (132).

Lupus Satisfaction Questionnaire (LSQ) was recently developed to evaluate SLE patients treatment satisfaction and to help informing them about treatment decisions (133). The same authors have also developed a questionnaire (Systemic Lupus Erythematosus Steroid Questionnaire) that specifically wants to improve the understanding of the benefits and the burdens of steroids for SLE patients (134). Both these instruments, if further validated, may help to improve patients' adherence to therapy.

In conclusion, a better understanding of patients' disease experiences is crucial. Last year new data confirmed that HRQoL has to be considered an independent outcome measure and, as such, has to be routinely evaluated in SLE patients.

Conclusion

2017 was a year full of new and interesting findings about a complex and heterogeneous disease like SLE. This review summarised the most relevant articles published last year regarding SLE pathogenesis, clinical and laboratory features as well as comorbidities and novel treatments.

However, this is an overview of the most interesting news provided in the literature on a disease that, for various aspects, remains challenging: there is a growing need for studies and research which could improve the understanding of SLE in order to lead to a better management of the disease.

References

1. LA PAGLIA GMC, LEONE MC, LEPRI G *et al.*: One year in review 2017: systemic lupus erythematosus. *Clin Exp Rheumatol* 2017; 35: 551-61.
2. MURAYAMA G, FURUSAWA N, CHIBA A *et al.*: Enhanced IFN-α production is associated with increased TLR7 retention in the lysosomes of palasmacytoid dendritic cells in systemic lupus erythematosus. *Arthritis Res Ther* 2017; 19: 234.
3. YUAN Y, YANG M, WANG K *et al.*: Excessive activation of the TLR9/TGF-β1/PDGF-B pathway in the peripheral blood of patients with systemic lupus erythematosus. *Arthritis Res Ther* 2017; 19: 70.
4. ELLOUMI N, FAKHFAKH R, AYADI L *et al.*: The increased expression of Toll-Like Receptor 4 in renal and skin lesions in lupus erythematosus. *J Histochem Cytochem* 2017; 65389-398.
5. PAN Q, FENG Y, PENG Y *et al.*: Basophil recruitment to skin lesions of patients with systemic lupus erythematosus mediated by CCR1 and CCR2. *Cell Physiol Biochem* 2017; 43: 832-39.
6. ROTHER N, PIETERSE E, LUBBERS J *et al.*: Acetylated histones in apoptotic microparticles drive the formation of neutrophil extracellular traps in active lupus nephritis. *Front immunol* 2017; 8: 1136.
7. VITALES-NOYOLA M, OCEQUERA-MALDONADO B, NIÑO-MORENO P *et al.*: Patients with systemic lupus erythematosus show increased levels and defective function of CD69⁺ T regulatory cells. *Mediators inflamm* 2017; 2017: 2513829.
8. LIU J, BERTHIER CC, KAHLENBERG JM: Enhanced inflammasome activity in systemic lupus erythematosus is mediated via

9. OLSSON LM, JOHANSSON AC, GULLSTRAND B *et al.*: A single nucleotide polymorphism in the NCF1 gene leading to reduced oxidative burst is associated with systemic lupus erythematosus. *Ann Rheum Dis* 2017; 76: 1607-13.
10. NIU Y, SENGUPTA M, TITOV AA *et al.*: The PBX1 lupus susceptibility gene regulates CD44 expression. *Mol imminol* 2017; 85: 148-54.
11. HONG KM, KIM HK, PARK SY *et al.*: CD3Z hypermethylation is associated with severe clinical manifestations in systemic lupus erythematosus and reduces CD3ζ-chain expression in T cells. *Rheumatology* (Oxford) 2017; 56: 467-76.
12. ZHOU A, LIU X, XIA T *et al.*: Estrogen receptor alpha gene (ESR1) polymorphism and its interaction with smoking and drinking contribute to susceptibility of systemic lupus erythematosus. *Immunol Res* 2017; 65: 951-56.
13. YOUNG KA, MUNROE ME, GUTHRIDGE JM *et al.*: Combined role of vitamin D status and CYP24A1 in the transition to systemic lupus erythematosus. *Ann Rheum Dis* 2017; 76: 153-58.
14. LOOD C, TYDÉN H, GULLSTRAND B *et al.*: Decreased platelet size is associated with platelet activation and anti-phospholipid syndrome in systemic lupus erythematosus. *Rheumatology* (Oxford) 2017; 56: 408-16.
15. FLECHSIG A, ROSE T, BARKHUDAROVA F *et al.*: What is the clinical significance of anti-Sm antibodies in systemic lupus erythematosus? A comparison with anti-dsDNA antibodies and C3. *Clin Exp Rheumatol* 2017; 35: 598-606.
16. SHAHIN D, EL-FARAHATY RM, HOUSSEN ME *et al.*: Serum 25-OH vitamin D level in treatment-naïve systemic lupus erythematosus patients: Relation to disease activity, IL-23 and IL-17. *Lupus* 2017; 26: 917-26.
17. DIVARD G, ABBAS R, CHENEVIER-GOBEAUX C *et al.*: High-sensitivity cardiac troponin T is a biomarker for atherosclerosis in systemic lupus erythematosus patients: a cross-sectional controlled study. *Arthritis Res Ther* 2017; 19: 132.
18. KIM KJ, BAEK IW, YOON CH *et al.*: Elevated levels of soluble CD40 ligand are associated with antiphospholipid antibodies in patients with systemic lupus erythematosus. *Clin Exp Rheumatol*. 2017; 35: 823-30.
19. WIRESTAM L, FRODLUND M, ENOCSSON H *et al.*: Osteopontin is associated with disease severity and antiphospholipid syndrome in well characterised Swedish cases of SLE. *Lupus Sci Med* 2017; 4.
20. XU B, WANG S, ZHOU M *et al.*: The ratio of circulating follicular T helper cell to follicular T regulatory cell is correlated with disease activity in systemic lupus erythematosus. *Clin Immunol* 2017; 183: 46-53.
21. CHIBA A, TAMURA N, YOSHIKIYO K *et al.*: Activation status of mucosal-associated invariant T cells reflects disease activity and pathology of systemic lupus erythematosus. *Arthritis Res Ther* 2017; 19: 58.

22. WEN S, HE F, ZHU X *et al.*: IFN-γ, CXCL16, uPAR: potential biomarkers for systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 36-43.

23. ROSE T, GRÜTZKAU A, KLOTSCHE J *et al.*: Are interferon-related biomarkers advantageous for monitoring disease activity in systemic lupus erythematosus? A longitudinal benchmark study. *Rheumatology* (Oxford) 2017; 56: 1618-26.

24. AGGARWAL A, GUPTA R, NEGI VS *et al.*: Urinary haptoglobin, alpha-1 anti-chymotrypsin and retinol binding protein identified by proteomics as potential biomarkers for lupus nephritis. *Clin Exp Immunol* 2017; 188: 254-62.

25. LA'ULU SL, SUH-LAILAM BB, DAVIS KW *et al.*: Comparative analysis of neutrophil gelatinase-associated lipocalin and other laboratory markers for lupus nephritis: a cross-sectional investigation. *Ann Clin Biochem* 2017; 54: 240-45.

26. ŽIVKOVIĆ V, CVETKOVIĆ T, MITIĆ B *et al.*: Monocyte chemoattractant protein-1 as a marker of systemic lupus erythematosus: an observational study. *Rheumatol Int* 2018; 38: 1003-08.

27. CARDENAS-GONZALEZ M, SRIVASTAVA A, PAVKOVIC M *et al.*: Identification, confirmation, and replication of novel urinary microRNA biomarkers in lupus nephritis and diabetic nephropathy. *Clin Chem* 2017; 63: 1515-26.

28. SKEOCH S, HUBBARD CRISTINACCE PL, DOBBS M *et al.*: Evaluation of non-contrast MRI biomarkers in lupus nephritis. *Clin Exp Rheumatol* 2017; 35: 954-58.

29. ODLER B, BIKOV A, STREIZIG J *et al.*: CCL21 and IP-10 as blood biomarkers for pulmonary involvement in systemic lupus erythematosus patients. *Lupus* 2017; 26: 572-79.

30. MASSARO L, CECCARELLI F, COLASANTI T *et al.*: Anti-carbamylated protein antibodies in systemic lupus erythematosus patients with articular involvement. *Lupus* 2018; 27: 105-11.

31. LENG X, LI M, LI X *et al.*: Chinese lupus treatment and research group (CSTAR) registry: X. family history in relation to lupus clinical and immunological manifestations. *Clin Exp Rheumatol* 2018; 36: 81-87.

32. SARBU N, TOLEDANO P, CALVO A *et al.*: Advanced MRI techniques: biomarkers in neuropsychiatric lupus. *Lupus* 2017; 26: 510-16.

33. RIVEROS FRUTOS A, CASAS I, RÚA-FIGUEROA I *et al.*: Systemic lupus erythematosus in Spanish males: a study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. *Lupus* 2017; 26: 698-706.

34. NG R, BERNATSKY S, RAHME E: Disease characterization of systemic lupus erythematosus (SLE) patients in Quebec. *Lupus* 2017; 26: 1005-11.

35. AHMED N, SHIGIDI M, AL AGIB AN *et al.*: Clinical features and antinuclear antibodies profile among adults with systemic lupus erythematosus and lupus nephritis: a cross-sectional study. *Pan Afr Med J* 2017; 27: 114.

36. LI WG, YE ZZ, YIN ZH *et al.*: Clinical and immunological characteristics in 552 systemic lupus erythematosus patients in a southern province of China. *Int J Rheum Dis* 2017; 20: 68-75.

37. CANORA J, GARCÍA M, MITJAVILA F *et al.*: Clinical characteristics during diagnosis of a prospective cohort of patients with systemic lupus erythematosus treated in Spanish Departments of Internal Medicine: The RELES study. *Rev Clin Esp* 2017; 217: 7-14.

38. TORRENTE-SEGARRA V, SALMAN MONTE TC, RÚA-FIGUEROA I *et al.*: Juvenile- and adult-onset systemic lupus erythematosus: a comparative study in a large cohort from the Spanish Society of Rheumatology Lupus Registry (RELESSER). *Clin Exp Rheumatol* 2017; 35: 1047-55.

39. TOLEDANO P, ORUETA R, RODRÍGUEZ-PINTÓ I *et al.*: Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre. *Autoimmun Rev* 2017; 16: 750-55.

40. QUINTANILLA-GONZÁLEZ L, ATISHA-FREGOSO Y, LLORENTE L *et al.*: Myelitis in systemic lupus erythematosus: clinical characteristics and effect in accrual damage. A single-center experience. *Lupus* 2017; 26: 248-54.

41. WATAD A, TIOSANO S, BRAGAZZI NL *et al.*: Epilepsy among systemic lupus erythematosus patients: insights from a large database analysis. *Neuroepidemiology* 2018; 50: 1-6.

42. ARKEMA EV, SVENUNGSSON E, VON EULER M *et al.*: Stroke in systemic lupus erythematosus: a Swedish population-based cohort study. *Ann Rheum Dis* 2017; 76: 1544-49.

43. COHEN D, RIJNINK EC, NABUURS RJ *et al.*: Brain histopathology in patients with systemic lupus erythematosus: identification of lesions associated with clinical neuropsychiatric lupus syndromes and the role of complement. *Rheumatology* (Oxford) 2017; 56: 77-86.

44. PARK DJ, KANG JH, LEE KE *et al.*: Association of depression with socioeconomic status, anticardiolipin antibodies, and organ damage in patients with systemic lupus erythematosus: results from the KORNET registry. *Clin Exp Rheumatol* 2018 Feb 14 [Epub ahead of print].

45. THOMAS G, COHEN AUBART F, CHICHE L *et al.*: Lupus myocarditis: initial presentation and longterm outcomes in a multicentric series of 29 patients. *J Rheumatol* 2017; 44: 24-32.

46. MOK CC, TSE SM, CHAN KL *et al.*: Effect of the metabolic syndrome on organ damage and mortality in patients with systemic lupus erythematosus: a longitudinal analysis. *Clin Exp Rheumatol* 2018; 36: 389-95.

47. HAYE SALINAS MJ, CAEIRO F, SAURIT V *et al.*: Pleuropulmonary involvement in patients with systemic lupus erythematosus from a Latin American inception cohort (GLADEL). *Lupus* 2017; 26: 1368-77.

48. HAJJI M, HARZALLAH A, KAAROUD H *et al.*: Factors associated with relapse of lupus nephritis: a single center study of 249 cases.

Saudi J Kidney Dis Transpl 2017; 28: 1349-55.

49. TEKE HÜ, CANSU DÜ, KORKMAZ C: Detailed features of hematological involvement and medication-induced cytopenia in systemic lupus erythematosus patients: single center results of 221 patients. *Eur J Rheumatol* 2017; 4: 87-92.

50. AZRIELANT S, TIOSANO S, WATAD A *et al.*: Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study. *Immunol Res* 2017; 65: 464-69.

51. GAO N, LI MT, LI YH *et al.*: Retinal vasculopathy in patients with systemic lupus erythematosus. *Lupus* 2017; 26: 1182-89.

52. SHENAVANDEH S, HABIBI S: Nailfold capillaroscopic changes in patients with systemic lupus erythematosus: correlations with disease activity, skin manifestation and nephritis. *Lupus* 2017; 26: 959-66.

53. LIM CC, LIU PY, TAN HZ *et al.*: Severe infections in patients with lupus nephritis treated with immunosuppressants: a retrospective cohort study. *Nephrology* 2017; 22: 478-84.

54. CHEN HL, SHEN LJ, HSU PN *et al.*: Cumulative burden of glucocorticoid-related adverse events in patients with systemic lupus erythematosus: findings from a 12-year longitudinal study. *J Rheumatol* 2018; 45: 83-89.

55. FELDMAN CH, MARTY FM, WINKELMAYER WC *et al.*: Comparative rates of serious infections among patients with systemic lupus erythematosus receiving immunosuppressive medications. *Arthritis Rheumatol* 2017; 69: 387-97.

56. ZHAN Z, LAO M, SU F *et al.*: Hospital-acquired infections in patients with systemic lupus erythematosus: a case-control study in a southern Chinese population. *Clin Rheumatol* 2018; 37: 709-17.

57. AZRIELANT S, TIOSANO S, WATAD A *et al.*: Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study. *Immunol Res* 2017; 65: 464-69.

58. HSU CY, LIN MS, SU YJ *et al.*: Cumulative immunosuppressant exposure is associated with diversified cancer risk among 14 832 patients with systemic lupus erythematosus: a nested case-control study. *Rheumatology* (Oxford) 2017; 56: 620-28.

59. WADSTROM H, ARKEMA EV, SJOWALL C *et al.*: Cervical neoplasia in systemic lupus erythematosus: a nationwide study. *Rheumatology* (Oxford) 2017; 56: 613-19.

60. FELDMAN CH, LIU J, FELDMAN S *et al.*: Risk of high-grade cervical dysplasia and cervical cancer in women with systemic lupus erythematosus receiving immunosuppressive drugs. *Lupus* 2017; 26: 682-89.

61. BERNATSKY S, VELASQUEZ GARCIA HA, SPINELLI JJ *et al.*: Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma. *Lupus Sci Med* 2017; 4: e000187.

62. WATAD A, TIOSANO S, AZRIELANT S *et al.*: Low levels of calcium or vitamin D - which is more important in systemic lupus erythematosus patients? An extensive data analysis. *Clin Exp Rheumatol*. 2017; 35: 108-12.

63. NEVSKAYA T, GAMBLE MP, POPE JE: A meta-analysis of avascular necrosis in systemic lupus erythematosus: prevalence and risk factors. *Clin Exp Rheumatol* 2017; 35: 700-10.

64. GUO Q, FAN P, LUO J *et al.*: Assessment of bone mineral density and bone metabolism in young male adults recently diagnosed with systemic lupus erythematosus in China. *Lupus* 2017; 26: 289-93.

65. GARCIA-CARRASCO M, MENDOZA-PINTO C, LEO-N-VAZQUEZ ML *et al.*: Incidence of vertebral fractures in women with systemic lupus erythematosus after 8 years of follow up. *Calcif Tissue Int May* 2017; 101: 291-99.

66. TSELIOS K, GLADMAN DD, SU J *et al.*: Evolution of risk factors for atherosclerotic cardiovascular events in systemic lupus erythematosus: a longterm prospective study. *J Rheumatol* 2017; 44: 1841-49.

67. TEKTONIDOU MG, KRAVVARITI E, KONSTANTONIS G *et al.*: Subclinical atherosclerosis in systemic lupus erythematosus: comparable risk with diabetes mellitus and rheumatoid arthritis. *Autoimmun Rev* 2017; 16: 308-12.

68. GUSTAFFSON JT, HERLITZ LINDBERG M, GUNNARSSON I *et al.*: Excess atherosclerosis in systemic lupus erythematosus, - A matter of renal involvement: Case control study of 281 SLE patients and 281 individually matched population controls. *PLoS One* 2017; 12: e0174572.

69. ARKEMA EV, SVENUNGSSON E, VON EULER M *et al.*: Stroke in systemic lupus erythematosus: a Swedish population-based cohort study. *Ann Rheum Dis* 2017; 76: 1544-49.

70. SÁNCHEZ-PÉREZ H, TEJERA-SEGURA B, DE VERA-GONZÁLEZ A *et al.*: Insulin resistance in systemic lupus erythematosus patients: contributing factors and relationship with subclinical atherosclerosis. *Clin Exp Rheumatol* 2017; 35: 885-92.

71. STOHL W, SCHWARTING A, OKADA M *et al.*: Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. *Arthritis Rheumatol* 2017; 69: 1016-27.

72. TOUMA Z, SAYANI A, PINEAU CA *et al.*: Belimumab use, clinical outcomes and glucocorticoid reduction in patients with systemic lupus erythematosus receiving belimumab in clinical practice settings: results from the OBSErve Canada study. *Rheumatol Int* 2017; 37: 865-73.

73. STHOEGER Z, LORBER M, TAL Y *et al.*: Anti-BLyS treatment of 36 Israeli systemic lupus erythematosus patients. *Isr Med Assoc J* 2017; 19: 44-48.

74. PARODIS I, SJ-OWALL C, J-ONSEN A *et al.*: Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus. *Autoimmun Rev* 2017; 16: 343-351.

75. NAGEL J, SAXNE T, GEBOREK P *et al.*: Treatment with belimumab in systemic lupus erythematosus does not impair antibody response to 13-valent pneumococcal conjugate vaccine. *Lupus* 2017; 26: 1072-81.

76. CHATHAM W, CHADHA A, FETTIPLACE J *et al.*: A randomized, open-label study to investigate the effect of belimumab on pneumococcal vaccination in patients with active, autoantibody-positive systemic lupus erythematosus. *Lupus* 2017; 26: 1483-90.

77. LENERT A, NIEWOLD TB, LENERT P: Spotlight on blisibimod and its potential in the treatment of systemic lupus erythematosus: evidence to date. *Drug Des Devel Ther* 2017; 11: 747-57.

78. FURIE RA, LEON G, THOMAS M *et al.*: A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. *Ann Rheum Dis* 2015; 74: 1667-75.

79. MERRILL JT, SHANAHAN WR, SCHEINBERG M *et al.*: Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018; 77: 883-89.

80. DALL'ERA M, CHAKRAVARTY E, WALLACE D *et al.*: Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. *Arthritis Rheum* 2007; 56: 4142-50.

81. ISENBERG D, GORDON C, LICU D *et al.*: Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data *Ann Rheum Dis* 2015; 74: 2006-15.

82. GORDON C, WOFSY D, WAX S *et al.*: Post hoc analysis of the phase II/III APRIL-SLE Study: association between response to Atacicept and serum biomarkers including BLyS and APRIL. *Arthritis Rheumatol* 2017; 69: 122-30.

83. MERRILL JT, WALLACE DJ, WAX S *et al.*: Safety of Atacicept in patients with systemic lupus erythematosus: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. *Arthritis Rheum* 2018; 70: 266-76.

84. KYTTARIS VC: Novel Treatments in Lupus. *Curr Rheumatol Rep* 2017; 19: 10.

85. CARTER LM, ISENBERG DA, EHRENSTEIN MR: Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum* 2013; 65: 2672-79.

86. CHAVAROT N, VERHELST D, PARDON A *et al.*: Rituximab alone as induction therapy for membranous lupus nephritis: A multicenter retrospective study. *Medicine* (Baltimore) 2017; 96: e7429.

87. GRACIA-TELLO B, EZEONYEJI A, ISENBERG D: The use of rituximab in newly diagnosed patients with systemic lupus erythematosus: long-term steroid saving capacity and clinical effectiveness. *Lupus Sci Med* 2017; 4: e000182.

88. REDDY V, MARTINEZ L, ISENBERG DA *et al.*: Pragmatic treatment of patients with systemic lupus erythematosus with Rituximab: long-term effects on serum immunoglobulins. *Arthritis Care Res* (Hoboken) 2017; 69: 857-66.

89. YUSOF MY, SHAW D, EL-SHERBINY YM *et al.*: Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. *Ann Rheum Dis* 2017; 76: 1829-36.

90. CLOWSE ME, WALLACE DJ, FURIE RA *et al.*: Efficacy and safety of Epratuzumab in moderately to severely active systemic lupus erythematosus: results from two phase III randomized, double-blind, placebo-controlled trials. *Arthritis Rheumatol* 2017; 69: 362-75.

91. ZHANG H, LIU Z, HUANG L *et al.*: The short-term efficacy of bortezomib combined with glucocorticoids for the treatment of refractory lupus nephritis. *Lupus* 2017; 26:952-58.

92. PSARRAS A, EMERY P, VITAL EM: Type I interferon-mediated autoimmune diseases: pathogenesis, diagnosis and targeted therapy. *Rheumatology* (Oxford) 2017; 56: 1662-75.

93. BENGTSSON AA, RÖNNBLOM L: Role of interferons in SLE. *Best Pract Res Clin Rheumatol* 2017; 31: 415-28.

94. KHAMASHTA M, MERRILL JT, WERTH VP *et al.*: Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016; 75: 1909e16.

95. GRETH W, ROBBIE GJ, BROHAWN P: Targeting the interferon pathway with sifalimumab for the treatment of systemic lupus erythematosus. *Immunotherapy* 2017; 9: 57-70.

96. FURIE R, KHAMASHTA M, MERRILL JT *et al.*: Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis Rheumatol* 2017; 69: 376-86.

97. SHEIKHOLESLAMIA M, HAJIALILOA M, SADREDDIN RASI HASHEMIB S *et al.*: Low dose cyclosporine A in the treatment of resistant proliferative lupus nephritis. *Mod Rheumatol* 2018; 28: 523-29.

98. SAKAI R, KURASAWA T, NISHI E *et al.*: Efficacy and safety of multitarget therapy with cyclophosphamide and tacrolimus for lupus nephritis: a prospective, single-arm, single-centre, open label pilot study in Japan. *Lupus* 2018; 27: 273-82.

99. KAMANAMOOL N, INGSATHIT A, RATTANASIRI S *et al.*: Comparison of disease activity between tacrolimus and mycophenolate mofetil in lupus nephritis: a randomized controlled trial. *Lupus* 2018; 27: 647-56.

100. WALLACE DJ, STRAND V, MERRILL JT *et al.*: Efficacy and safety of an interleukin 6 monoclonal antibody for the treatment of systemic lupus erythematosus: a phase II dose-ranging randomised controlled trial. *Ann Rheum Dis* 2017; 76: 534-42.

101. ROMERO-MATÉ A, GARCÍA-DONOSO C, HERNÁNDEZ-NÚÑEZ A *et al.*: Successful treatment of recalcitrant discoid lupus erythematosus with ustekinumab. *Dermatol Online J* 2017; 15: 23.

102. LENG XM, JIANG Y, ZHOU DB *et al.*: Good outcome of severe lupus patients with high-dose immunosuppressive therapy and autologous peripheral blood stem cell transplan-

tation: a 10-year follow-up study. *Clin Exp Rheumatol* 2017; 35: 494-99.

103. DENG D, ZHANG P, GUO Y *et al.*: A randomised double-blind, placebo-controlled trial of allogeneic umbilical cord-derived mesenchymal stem cell for lupus nephritis. *Ann Rheum Dis* 2017; 76: 1436-39.

104. ZAHI T, DAFNA DG: Current and future therapies for SLE: obstacles and recommendations for the development of novel treatments. *Lupus Sci Med* 2017; 4: e000239.

105. MOSCA M, TANI C, ARINGER M *et al.*: European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis* 2010; 69: 1269-74.

106. MORGAN C, BLAND AR, MAKER C *et al.*: Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. *Lupus* 2018; 27: 681-87.

107. KENT T, DAVIDSON A NEWMAN D *et al.*: Burden of illness in systemic lupus erythematosus: results from a UK patient and carer online survey. *Lupus* 2017; 26: 1095-100.

108. PASCUAL-RAMOS V, CONTRERAS-YANEZ I, VALENCIA-QUINONES KR, ROMERO-DÍAZ J: Rheumatoid arthritis patients achieved better quality of life than systemic lupus erythematosus patients at sustained remission. *Clin Exp Rheumatol* 2018; 36: 619-26.

109. CHAIGNE B, FINCKH A, ALPIZAR-RODRIGUEZ D *et al.*: Differential impact of systemic lupus erythematosus and rheumatoid arthritis on health-related quality of life. *Qual Life Res* 2017; 26: 1767-75.

110. CHAIGNE B, CHIZZOLINI C, PERNEGER T *et al.*: Impact of disease activity on health-related quality of life in systemic lupus erythematosus - a cross-sectional analysis of the Swiss Systemic Lupus Erythematosus Cohort Study (SSCS). *BMC Immunol* 2017; 18: 17.

111. GOLDER V, KANDANE-RATHNAYAKE R, HOI AY *et al.*: Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. *Arthritis Res Ther* 2017; 19: 62.

112. MOK CC, HO LY, TSE SM *et al.*: Prevalence of remission and its effect on damage and quality of life in Chinese patients with systemic lupus erythematosus. *Ann Rheum Dis* 2017; 76: 1420-25.

113. JOLLY M, TOLOZA S, GOKER B *et al.*: Disease-specific quality of life in patients with lupus nephritis. *Lupus* 2018; 27: 257-64.

114. MONAHAN RC, BEAART-VAN DE VOORDE LJJ, STEUP-BEKMAN GM *et al.*: Neuropsychiatric symptoms in systemic lupus erythematosus: impact on quality of life. *Lupus* 2017; 26: 1252-59.

115. PIGA M, CONGIA M, GABBA A *et al.*: Musculoskeletal manifestations as determinants of quality of life impairment in patients with systemic lupus erythematosus. *Lupus* 2018; 27: 190-98.

116. TANI C, CARLI L, DELLE SEDIE A *et al.*: Impact of joint involvement on patients reported outcomes in systemic lupus erythematosus. *Curr Rheumatol Rev* 2017 Mar 14 [Epub ahead of print].

117. CALDERÓN J, FLORES P, AGUIRRE JM *et al.*: Impact of cognitive impairment, depression, disease activity, and disease damage on quality of life in women with systemic lupus erythematosus. *Scand J Rheumatol* 2017; 46: 273-80.

118. YILMAZ-ONER S, IILAN B, CAN M *et al.*: Fatigue in systemic lupus erythematosus: Association with disease activity, quality of life and psychosocial factors. *Z Rheumatol* 2017; 76: 913-19.

119. MORALEDA V, PRADOS G, MARTINEZ MP *et al.*: Sleep quality, clinical and psychological manifestations in women with systemic lupus erythematosus. *Int J Rheum Dis* 2017; 20: 1541-50.

120. MAZZONI D, CICOGNANI E, PRATI G: Health-related quality of life in systemic lupus erythematosus: a longitudinal study on the impact of problematic support and self-efficacy. *Lupus* 2017; 26: 125-31.

121. GOLDER V, OOI JJY, ANTONY AS *et al.*: Discordance of patient and physician health status concerns in systemic lupus erythematosus. *Lupus* 2018; 27: 501-6.

122. PETTERSSON S, SVENUNGSSON E, GUSTAFSSON J *et al.*: A comparison of patients' and physicians' assessments of disease activity using the Swedish version of the Systemic Lupus Activity Questionnaire. *Scand J Rheumatol* 2017; 46: 474-83.

123. EL MIEDANY Y, EL GAAFARY M, EL AROUSSY N *et al.*: Toward electronic health recording: evaluation of electronic patient reported outcome measures (e-PROMs) system for remote monitoring of early systemic lupus patients. *Clin Rheumatol* 2017; 36: 2461-69.

124. BABA S, KATSUMATA Y, OKAMOTO Y *et al.*: Reliability of the SF-36 in Japanese patients with systemic lupus erythematosus and its associations with disease activity and dam-

age: a two-consecutive year prospective study. *Lupus* 2018; 27: 407-16.

125. KASTURI S, SZYMONIFKA J, BURKET JC *et al.*: Feasibility, validity, and reliability of the 10-item patient reported outcomes measurement information system global health short form in outpatients with systemic lupus erythematosus. *J Rheumatol* 2018; 45: 397-404.

126. NANTES SG, STRAND V, SU J *et al.*: Comparison of the sensitivity to change of the 36-item short form health survey and the lupus quality of life measure using various definitions of minimum clinically important differences in patients with active systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2018; 70: 125-33.

127. INOUE M, SHIOZAWA K, YOSHIHARA R *et al.*: The Japanese LupusPRO: A cross-cultural validation of an outcome measure for lupus. *Lupus* 2017; 26: 849-56.

128. AZIZODDIN DR, WEINBERG S, GANDHI N *et al.*: Validation of the LupusPRO version 1.8: an update to a disease-specific patient-reported outcome tool for systemic lupus erythematosus. *Lupus* 2018; 27: 728-37.

129. SCHNEIDER M, MOSCA M, PEGO-REIGOSA JM *et al.*: Cross-cultural validation of Lupus Impact Tracker in five European clinical practice settings. *Rheumatology* (Oxford) 2017; 56: 818-28.

130. BRANDT JE, DRENKARD C, KAN H *et al.*: External validation of the Lupus Impact Tracker in a southeastern US longitudinal cohort with systemic lupus Erythematosus. *Arthritis Care Res* (Hoboken) 2017; 69: 842-48.

131. ANTONY A, KANDANE-RATHNAYAKE RK, KO T *et al.*: Validation of the Lupus Impact Tracker in an Australian patient cohort. *Lupus* 2017; 26: 98-105.

132. DEVILLIERS H, BONITHON-KOPP C, JOLLY M *et al.*: The lupus impact tracker is responsive to changes in clinical activity measured by the systemic lupus erythematosus responder index. *Lupus* 2017; 26: 396-402.

133. MATHIAS SD, BERRY P, PASCOE K *et al.*: Treatment satisfaction in systemic lupus erythematosus: development of a patient-reported outcome measure. *J Clin Rheumatol* 2017; 23: 94-10.

134. MATHIAS SD, BERRY P, DE DEVRIES J *et al.*: Development of the Systemic Lupus Erythematosus Steroid Questionnaire (SSQ): a novel patient-reported outcome tool to assess the impact of oral steroid treatment. *Health Qual Life Outcomes* 2017; 15: 43.