LUPUS WHITE BOOK

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Index

Introduction

With several recent drug approvals, the field of Systemic Lupus Erythematosus (SLE) is evolving more rapidly than ever before. As new research data and clinical experience expand our knowledge of this rare autoimmune disease, this *first Edition* of the **Lupus White Book by SLEuro** provides state-of-the-art strategies for the diagnosis and treatment of SLE, as well as comprehensive information about the numerous challenges and unmet needs that remain to be faced for improving the care of SLE.

The **Lupus White Book** is the latest reference for anyone, lupus patients and patient associations, basic science or translational researchers, medical doctors, medical students, nurses and other healthcare professionals, pharmaceutical companies and healthcare authorities involved in the care of SLE patients.

Taking a clinical, evidence-based approach, written by world-renowned SLEuro lupus experts who are at the forefront of each specific topic, and presented in a practical, bullet-point style, for rapid reference, this *first edition* of the **Lupus White Book** is a definitive source of trusted content and a major reference book for all those interesting the complex field of SLE.

The **Lupus White Book** is fully available online. Practically structured, each chapter is short and presented critically with selected key references. The **Lupus White Book** focuses first on the key determinants of SLE, our current understanding of its presenting symptoms and the evolving concept of early lupus, before reviewing advanced aspects and contemporary challenges for the diagnosis and treatment of SLE, including the development of digital medicine.

This **Lupus White Book** would not have been made possible without the generous support of our sponsors and the admirable contribution of internationally renowned lupus experts, as well as that of the SLEuro secretariat team. I would like to thank them personally and acknowledge their outstanding work and support. We are enthusiastic about this first Edition and hope that you will find the **Lupus White Book** a significant contribution to raise high-level knowledge and lupus awareness.

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Genetics and Genomics of SLE, Stratification of SLE

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Context

The combinations of several new technologies and analysis algorithms and methods has made it possible to advance rapidly in the knowledge regarding the genetic susceptibility and genetic causes of SLE, but also to molecularly define patients in a determined disease state. Also more in-depth analysis has been made possible thanks to the singe cell sequencing with multiple potential possibilities that may discern in detail genomic and epigenomic mechanisms of disease.

Key findings

The past decade has seen tremendous development in genetics, genomics and machine learning. In the field of rare connective tissue diseases, including SLE. These opportunities enable numerous innovative applications:

- Genetic susceptibility, knowledge of the additive effects of the more than 80 genes associated with SLE today and with genetic risk analysis may provide a picture of an individual patient that could be used for prediction modeling.
- Transcriptomics and epigenomics, where molecular signatures may reveal the particular pathways a patient has during flares and the best medication to be used, this combined with machine learning. Mechanisms of genomic regulation of genes and the signatures.
- Deep phenotyping, prognostic modeling & precision medicine, in which integration of big data sets generated from well-defined SLE cohorts using high-level technological platforms (multi-omics) may help to elucidate underlying disease mechanisms and fuel precision medicine [1].
- Patients' perspective & engagement. The fear that family and children may develop the disease makes the genetics studies important particularly in the case of monogenic and rare mutations or autoinflammatory syndromes similar to the disease[2].

Main challenges

The study of genomics and genetics has been moving very rapidly. Better phenotyping of the patients and large cohorts of patients is necessary to identify the main genetic causes. SLE is most probably a group of diseases with a similar phenotype but with several underlying causes. It is most important to study patients in much more detail, to know their nutritional and dietary situation because the interaction between genes and environment is key to fully understand the mechanisms of the disease[3]. The design of genomics studies in clinical trials with data openly available would even help the pharmaceutical industry and

save years of work by using molecular signatures to define the type of patients and which may respond to the therapy. The number of patients not fulfilling the clinical diagnosis of SLE is tremendously high, and are patients that do have molecular signatures compatible with SLE or other systemic autoimmune diseases[4-6]. The molecular signatures could become, if well adapted and validated, the new approach to diagnose and properly treat patients instead of using a clinical term or clinical criteria. Machine learning methods are capable of using transcriptome signatures to predict when a patient may flare or stay in remission much earlier than clinical assessment. Assays and computational models to rapidly assess a patient would need to be accessible and available in the clinical practice.

Main unmet needs

- Complete and careful phenotyping of SLE patients
- Consider in the studies patients that do not fulfill the clinical criteria but years without diagnosis despite symptomatology. The diagnosis is the least important, treatment is crucial.
- Increased involvement of clinical practitioners in the understanding of genomics and molecular signatures for precision medicine practice

Perspectives

To achieve the full potential of genomics and the utility of molecular signatures in the clinical practice, physicians should become engaged in biostatistics and bioinformatics to learn machine learning methods and understand the methodology and the potential solutions. The use should be with care, always understanding the potential of overfitting and the best use of the tools.

Genetics studies are identifying the causal mutations and polymorphisms.

Genomics approaches offer new solutions not only in the clinic or in the pharmaceutic industry but also in research where enormous advances have been accomplished.

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Diagnosis of SLE

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Context

Due to its phenotypic heterogeneity, SLE often poses significant diagnostic challenges. The diagnosis of lupus can be considered in patients seen in various clinical settings such as in primary care, rheumatology clinics, hospital wards (as inpatients) or even in Intensive Care Units. In this respect, SLE patients may be evaluated first by non-rheumatology disciplines (e.g., dermatologists, neurologists, internists) before a conclusive diagnosis is reached. Importantly, correct and timely diagnosis is critical to ensure appropriate treatment and prevent disease complications. From the patient standpoint, diagnostic delays are linked to increased anxiety and unnecessary referrals.

The diversity of lupus clinical manifestations

As the prototype systemic autoimmune disease, SLE can present with a wide array of symptoms, signs and pathologies from multiple organs. An exhaustive review of lupus manifestations is outside the score of this chapter. **Mucocutaneous involvement** is highly prevalent, especially the characteristic malar ('butterfly') and maculopapular, subacute (psoriasiform and/or annular polycyclic non-scarring lesions), and chronic discoid rashes. Clinicians should also be mindful of a variety of other lupus-typical (e.g., chilblain lupus) and atypical (e.g., periungual erythema) rashes which can facilitate diagnosis in the appropriate setting. Often, lupus rashes are distributed on sun-exposed areas including the face, earlids, upper trunk and arms. Raynaud's phenomenon can be found in approximately 30% of patients but without digital ulcers. Alopecia (excessive, reversible hair loss) is common after other causes have been excluded, involving the scalp, eyebrows and other body parts, and is non-scarring with the exception of underlying discoid skin lupus. Mucosal membranes can be affected with ulcers, which are typically less severe than those in Adamantiades-Behcet's and are located on the buccal, nasal mucosa or the palate.

Musculoskeletal manifestations develop in the majority of SLE patients and include arthralgias, generalized stiffness, tenosynovitis but importantly, symmetric polyarthritis of the small joints and knees that can range from mild to severe, rheumatoid arthritis-like arthritis. Inflammatory myositis (5-15% of patients) affects the proximal muscles of lower and/or upper extremities but can also present with mild, subclinical elevation of muscle enzymes. In terms of **respiratory features**, pleuritis (with or without effusion, usually bilateral) is common, whereas acute pneumonitis (presenting as non-resolving infectious pneumonia) is found in less than 5% and can sometimes result in interstitial lung disease which is however, of mild-to-moderate severity. Alveolar hemorrhage due to pulmonary capillaritis is a rare, life-threatening condition. Pulmonary hypertension is increasingly recognized as a complication of long-standing, moderate or severe lupus. **Cardiovascular features** include pericarditis (20–30%), infrequently resulting in cardiac tamponade, and myocarditis with elevated cardiac enzymes, left ventricular wall motion abnormalities and

dysfunction. Venous or arterial thrombotic events may occur, especially in the setting of positive antiphospholipid antibodies or enhanced disease activity.

The gastrointestinal system is affected in some patients with SLE with clinically relevant manifestations including hepatitis ('lupoid'), which is less progressive than autoimmune hepatitis, ascites, protein-losing enteropathy and mesenteric vasculitis. Hematological manifestations are very common, especially leukopenia due to lymphopenia and/or neutropenia (usually in the range of absolute neutrophil count 1000-1500/μL). Anemia is mostly due to chronic inflammation with autoimmune hemolysis affecting 5-10% of patients. Thrombocytopenia is often the presenting manifestation of lupus and can range from mild to severe, life-threatening. Its coexistence with microangiopathic hemolytic anemia should alert physicians towards thrombotic thrombocytopenic purpura (TTP). Lymphadenopathy (regional or generalized) and splenomegaly, often accompanied by constitutional symptoms, are also common and need careful evaluation to exclude lymphoma.

Kidneys are affected in 40–50% of SLE patients although biopsy-proven, clinically relevant nephritis is less common (20–30%). Proteinuria above 0.5 g/24h, especially in the context of glomerular hematuria (active urine sediment) and/or impaired renal function, mandates for a diagnostic kidney biopsy since there is poor correlation between clinical and histological findings. Patients can manifest a broad spectrum of central and peripheral nervous **system disorders**, which however, are not specific to lupus and require exclusion of other causes. Their pathogenesis may be inflammatory and/or thrombotic, the latter especially in the context of positive antiphospholipid antibodies. The final attribution of neuropsychiatric events to SLE or not will depend on integrated assessment of patient history, disease activity, neuroimaging and/or other complementary tests. Finally, **ophthalmologic features** (excluding optic neuritis) of SLE include corneal/conjunctiva involvement (often due to secondary Sjogren's) and less frequently, uveitis, (epi)scleritis and retinal vasculitis.

Serological features of SLE

Less than 2% of SLE patients are truly negative for antinuclear antibodies (ANAs) at titers of 1:40, however, ANA negative rates can be somewhat higher at early disease stage or due to technical issues. The gold standard for ANA detection is by indirect immunofluorescence assay (IFA) using Hep-2 (or Hep-2000) cell line as substrate. ANAs lack disease specificity with the dense fine speckled (DFS) pattern and associated anti-DFS70 autoantibodies being often detected in healthy individuals. The immunological hallmark of SLE is autoantibodies directed against double stranded(ds) DNA, which display high specificity (>90–95%) for the disease. Serum anti-dsDNA levels tend to fluctuate with varying degrees of disease activity and there are multiple assays for their detection with the Farr and Crithidia luciliae immunofluorescence (CLIFT) tests capturing the high avidity antibodies. Anti-Sm (Smith) antibodies are found in 10–30% of patients and also show high specificity for SLE. Other antibodies to extractable nuclear antigens (ENAs) such as anti-RNP, anti-Ro/SSA, anti-La/SSB are common (up to 50%) but show less specificity. Notably, anti-Ro/SSA have been associated with photosensitive skin rashes, ANA-negative SLE and certain manifestations such as psychosis. About 20–25% of SLE patients have antiphospholipid (aPL) antibodies including anti-cardiolipin IgG/IgM, anti-β2-glycoprotein IgG/IgM and lupus anticoagulant. Considering their high prognostic relevance, all patients with probable or definitive SLE

should be screened for aPL antibodies. Numerous other autoantibodies (e.g., anti-ribosomal P, anti-C1q) are detected in SLE patients, however, their clinical utility remains limited. As a result of autoantibody-containing immunocomplexes, complement is consumed especially during the active phase of SLE, which results in reductions of serum fractions C3 and C4 (sensitivity and specificity rates in the range of 65–85%).

Classification criteria in SLE

Since 1971, the community has developed a number of classification criteria for SLE to assist the selection of appropriate patients in clinical studies. The 1997 criteria of the American College of Rheumatology (ACR) are the simplest and include 11 different clinical or immunological abnormalities. Despite their high specificity, drawbacks include the over-representation of skin manifestations, the vague definition of certain items (photosensitivity) and their suboptimal sensitivity for early disease. The 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria contain an extensive list of skin, neurological (e.g., myelitis) and immunological (e.g., low complement, positive Coombs in the absence of hemolysis) manifestations, thus enabling the early classification of additional patients at the expense, however of reduced specificity. Notably, patients with histologically-defined lupus nephritis and positive ANAs or anti-dsDNA are classified as SLE. More recently, the European Alliance of Associations for Rheumatology (EULAR) jointly with the ACR developed a new set of criteria introducing several new concepts: a) ANAs are treated as “entry criterion” and not counted as individual criterion, which helps to maintain a good balance between sensitivity and specificity, b) clinical and immunological manifestations are weighed variously according to their relevance to classification, c) in case there are multiple manifestations from the same organ/system, only the one with the highest weigh (score) counts, which helps to avoid over-representation, d) it is possible to classify patients on the basis of only a few high-yield features (e.g. arthritis and positive anti-DNA, membranous nephritis and low complement). Together, the 2019 EULAR/ACR criteria seem to have the best combination of high sensitivity (including for early disease) and specificity, thus can be a useful aid to clinicians evaluating a patient with possible connective tissue disease/SLE.

Biomarkers and other diagnostic approaches

Given the complexity of the disease and the diagnostic challenges, efforts have been put forward the identification of measurable biomarkers that can discriminate SLE from healthy individuals or patients with other diseases. The type I interferon pathway is profoundly active/overexpressed in SLE, including individuals at-risk, and interferon-related genes such as SIGLEC1 seem to have high diagnostic sensitivity. Urinary proteins such as CD163, NGAL, VCAM-1 are being evaluated for the diagnosis and monitoring of lupus kidney disease, still further standardization and validation is required. Blood transcriptome analysis based on hundreds of genes has demonstrated good sensitivity (86%) and specificity (92%) to classify SLE patients versus healthy counterparts. Recently, machine learning computational techniques have been applied on patient datasets in order to develop SLE diagnostic algorithms resembling clinical thinking. Although preliminary, some of the aforementioned approaches might eventually reach to clinical care supporting early diagnosis in uncertain or borderline cases.

Approach to SLE diagnosis

Patients who present with manifestations from at least two organs/systems (including the immunological) should be evaluated for possible SLE provided that other disorders (especially infections and malignancies) are excluded. Although developed for clinical trials, classification criteria can serve as a useful 'checklist' for physicians to screen for a variety of lupus-associated features, which are not better explained by another disease. The 2019 EULAR/ACR criteria have the best combination of sensitivity and specificity; for patients who score just below the classification threshold (e.g., 8 or 9) but clinical suspicion is high, the 2012 SLICC criteria can be applied and diagnosis be confirmed during follow-up. Caution should be exercised in severe organ-dominant disease (e.g., neurological, cytopenia) with limited immunological findings since such cases often represent "evolving lupus". In this scenario, patients can still receive a clinical diagnosis of SLE or be designated as "incomplete lupus" and be offered first-line treatment guided by the clinical presentation.

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Cutaneous manifestations

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Context

Mucocutaneous manifestations are amongst the most common in SLE, are prominent in diagnostic criteria and clinical trials, and are one of the three most common reasons to prescribe a targeted therapy (along with musculoskeletal and renal manifestations). The cutaneous organ system is among the most diverse in its features, including acute, subacute and discoid morphologies of rash, as well as alopecia, mucosal features and many rare forms. These features are highly impactful to patients. Recent evidence has demonstrated efficacy of new therapies, albeit varied between patients. Recent mechanistic insights demonstrate unique immunological processes underlying these features.

Key findings

- **Early experience with rituximab** demonstrated the potential for differential responses in cutaneous disease with some features responding well but others resistant to therapy or even worsening while patients were B cell depleted and other manifestations of lupus were improving. This observation suggests B cell independent inflammation in the skin, which may therefore explain resistance to therapy in many patients
- **Belimumab** which also targets B cells via BAFF was the first biologic therapy licensed for non-renal SLE and mucocutaneous features were prominent in the BLISS trials with more than 80% of patients affected at baseline. Results of those trials were analysed by organ specific features of the SLEDAI and BILAG instruments confirming efficacy in the main mucocutaneous items of rash, mucosal ulcers and alopecia with a comparable effect size to musculoskeletal features. However the number responding ranged from 45 to 64%, indicated significant numbers of patients resistant to this therapy
- **CLASI has become more prominent in SLE clinical trials**. The SLEDAI counts features as present or absent. It score a severe rash the same as mild and cannot capture partial change or worsening. The SLEDAI only awards 2 points for rash, so it is impossible to achieve the SRI-4 primary endpoint for rash alone. The BILAG-2004 does differentiate grades of severity, partial response and worsening, although still only has 4 possible levels (A-D). The CLASI was designed to solve these problems as a continuous outcome measure that rates each area of the body and differentiates activity from damage. Results from trials that use it (e.g. TULIP below) suggest it is a more sensitive outcome measure, differentiating treatment arms earlier and by a greater effect size.
- **Anifrolumab** which targets type I IFNs (IFN-I) is the second licensed therapy for non-renal SLE. Type I interferon pathway activation has a stronger association with mucocutaneous features than other manifestations of SLE. The TULIP studies included more organ-

specific outcome measures than the BLISS trials including the CLASI that demonstrate a relatively high degree of efficacy for mucocutaneous disease.

- **Mechanistic data** emphasise the importance of locally-produced IFN-I in the skin. Previous data had suggested that circulating immune cells were a key source of IFN-I. More recent data, including from pre-clinical phases of SLE, indicate that production of IFN-I by keratinocytes in the skin, exacerbated by UV light, predominates. This may explain why therapies that target haematopoietic immune cells are ineffective in some patients and therapies targeting non-haematopoietic innate immune mechanisms (including IFN-I) may benefit some patients more.
- **Experimental work** is beginning to elucidate how local immune mechanisms in the skin may contribute to causing a systemic disease. For example there are data on IFN production prior to onset of SLE, re-education of dendritic cells into a more immunogenic phenotype in the high IFN environment of the skin and transmigration of neutrophils between the skin and other organs after UV exposure in animal models.

Main challenges

Sophisticated approaches will be required to achieve good responses for all patients. The choice of therapeutic targets is broadening. While previous therapies mostly targeted B cells and other adaptive immune cells, those now under investigation cover a broader range of innate mechanisms including those only present in skin. This presents a challenge in translational studies and stratification with a greater requirement to study tissue and not just blood. Given the potential for different therapies to benefit some organs more than others or to benefit patients with certain underlying immunopathogenesic features, accurate capture of disease activity is a significant challenge. There has been a tendency in clinical trials and with regulators to rely on the SLEDAI in the understanding that it is easy to use. However, it does not meet the requirements for accurate clinical phenotyping. While tools like the CLASI are superior, acceptance by regulators is an issue. Cutaneous lupus falls under the care of both rheumatologists and dermatologists. Rheumatologists may not have specialist training to assess difficult skin disease in detail. In dermatology, some forms of cutaneous-only lupus are common outside SLE populations but awareness of therapies used by rheumatologists may be different. Extending data to these populations and engaging both specialties will be more important to implement new therapies.

Main unmet needs

- Accepted clinical tools to accurately measure different features of cutaneous disease and patient-reported outcomes
- A deeper understanding of mechanism of disease within tissue
- A greater range of therapeutic targets to address the large number of non-responders to existing therapies
- Increased and more logical uptake of effective new therapies across all relevant specialties

- Allowing patients to access the specialist care needed for complex clinical presentations and treatment decisions

Perspectives

The challenges of cutaneous manifestations exemplify many of the issues affecting SLE therapeutics as a whole. The heterogeneity of clinical features and response to therapy underline the need to accurately evaluate individual patients clinically and immunologically, and tailor therapies accordingly. Clear demonstration of benefit in targeted groups of high responders will also help meet the challenges of implementation of therapy in the clinic.

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Musculoskeletal manifestations

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Context

Musculoskeletal manifestations are well known to be among the most common features of SLE. These are diverse: the inflammatory features of synovitis and tenosynovitis are most prominent and amenable to therapy, but others include rare forms of deforming arthritis or avascular necrosis. Inflammatory musculoskeletal manifestations are the first presenting symptom in 50% of patients and affect 90% of patients at some time. Musculoskeletal manifestations are one of the three most common reasons for patients to receive a targeted therapy (along with mucocutaneous or renal) and one of the most common reasons for inclusion in clinical trials. Despite this, until relatively recently this aspect of SLE was poorly investigated with very little data on specific pathogenic mechanisms, or the assessment and therapy innovations that have revolutionized the management of inflammatory arthritis in other rheumatic diseases. This inequity is beginning to change with new research in SLE.

Key findings

- **Musculoskeletal symptoms were among the most bothersome** reported by patients in a 2020 European patient survey despite the best current therapy. Patients rated pain and / or swelling in joints the second most common symptom (77%) other than fatigue and the second most common (49.5%) symptom that they would like to go away.
- **Modern imaging** suggests that this symptom burden may be due to under-treatment. An ultrasound study showed that clinical instruments like joint swelling, BILAG and SLEDAI significantly underestimate objective musculoskeletal inflammation with 32% of symptomatic patients scoring on SLEDAI compared to 68% with significant inflammation on ultrasound, with the latter being associated with worse symptoms and serology even in the absence of joint swelling
- **Ultrasound inflammation is clinically relevant**: the multicentre longitudinal USEFUL study has reported that patients with ultrasound-proven inflammation exhibit better clinical response to therapy in terms of both symptoms and quality of life. However, this effect was only apparent when patients with fibromyalgia were excluded, suggesting that the latter have poor responses to lupus therapies even if they have proven musculoskeletal inflammation.
- **The SRI-4 outcome measure**, widely used in pivotal trials of new therapies, has been shown to be poorly responsive. SRI-4 non-responders have been shown to exhibit significant improvements in other musculoskeletal variables such as ultrasound following therapy
- **A new composite musculoskeletal disease activity instrument** similar to the DAS28 has been proposed: the Lupus Arthritis and Musculoskeletal Disease Activity Score (LAMDA).

This has been shown to increase in patients with ultrasound-proven inflammation in the absence of joint swelling, correlate with quality of life and treatment decision, and respond to therapy more than other tools.

- Immunopathogenic and translational studies in musculoskeletal inflammation in SLE are very limited. While a previous study indicated the presence of an interferon-signature in the synovial biopsies, recent studies have failed to demonstrate an association between musculoskeletal manifestations and the interferon signature that is used to stratify many SLE trials, in contrast to mucocutaneous manifestations. Thus the appropriateness of different classes of therapy for musculoskeletal disease is less clear

Main challenges

A unique aspect of this area of SLE research is that the challenges are also easily-realised opportunities. There are abundant lessons from inflammatory musculoskeletal features in other rheumatic diseases such as rheumatoid arthritis and psoriatic arthritis. These have provided transferrable knowledge that can be adapted to improve the care of SLE. Examples include methods to study synovial immunology, advanced imaging tools and a framework to include these in clinical research, a strong track record of more successful clinical trials, and widespread awareness of modern management strategies among rheumatologists. To realise these gains the greatest challenge is uptake of these innovations among trial sponsors and regulators.

Challenges may be greater for the non-inflammatory aspects of musculoskeletal symptoms in SLE where the background literature are weaker. Fibromyalgia is common in SLE populations and is well-known to be difficult to treat in any context. The pathology of complications such as deforming arthritis and avascular necrosis is poorly understood and there are no definitive treatments for these features. Differentiating these aspects of pathology is a key need for both physicians and patients.

Main unmet needs

- Understanding of the immunopathogenesis of musculoskeletal manifestations so that the most effective therapies can be developed and targeted to the most appropriate patients
- Clinical trial designs incorporating novel insights, such as focusing on musculoskeletal manifestations instead of multisystem SLE, recruiting patients with imaging proven synovitis and measuring responses using more sensitive and responsive outcome measures
- Clinical trials that better demonstrate the cost-effectiveness of therapies for this highly impactful manifestation
- Wider uptake of musculoskeletal imaging in routine practice to promote more appropriate prescribing of immunosuppressive therapy
- Therapeutic strategies to treat patients with non-inflammatory symptoms

Perspectives

While musculoskeletal disease has historically been understudied and undertreated in SLE, recent findings indicate that large gains in outcomes might be achieved relatively easily. The lupus community have identified the unmet need, the tools to measure this in practice, and potential trial designs that could provide clearer answers and larger effect sizes. While many classes of existing therapy have proven their value in musculoskeletal manifestations, the optimal implementation of these in healthcare systems requires more work. While the path to improving care of inflammatory symptoms is relatively clear, the best approach to non-inflammatory symptoms in SLE patients is less clear.

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Imaging of musculoskeletal manifestations in SLE

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Context

Imaging techniques play a major role in the diagnostic process of rheumatic diseases affecting the joints to support diagnosis, monitor treatment response and estimate disease progression. Radiographic imaging (X-ray) is reproducible, widely available and the standard outcome assessment in randomized clinical trials in inflammatory arthritis, especially in rheumatoid arthritis (RA), however, it is insensitive to detect inflammatory changes and has therefore a limited role in SLE. X-ray is used primarily for excluding other musculoskeletal diseases in differential diagnosis. By the use of the sensitive imaging modalities magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSUS) it is possible to clearly identify joints and tendons pathologies in SLE [1]. Both have become well-accepted standards for detecting early changes (such as early bone involvement (osteitis), synovitis, subcutaneous edema/swelling and tenosynovitis) and monitoring disease activity in patients with inflammatory arthritis (e.g., RA). In SLE, evidence on these techniques has emerged over the past decade, especially since up to 95% of SLE patients suffer from joint involvement [2], but they are less commonly used in clinical practice.

Key findings

- In MRI studies of SLE, synovitis is a frequent finding, particularly in the wrists and MCPs [1, 3].
- Also, tenosynovitis is reported by many different MRI studies in SLE [1, 3] – both for extensor and flexor tenosynovitis of the wrist [4] and also between the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints [1, 3].
- Comparing the distribution of bone erosions in patients with SLE or RA, the erosive burden detected by MRI is also present in SLE patients, though on a lower level (1.3 versus 3.4, p=0.004) [5].
- MSUS-detected synovitis and joint effusion in SLE are reported with high variability. In a systematic literature review of MSUS findings in SLE, synovitis and tenosynovitis are reported in 25% to 94% and 28% to 65% of patients, respectively, while power Doppler (PD) is reported in 10% to 82% of patients [6].
- Sixty-eight percent (60/88) of symptomatic patients have MSUS inflammation (grey-scale ≥2 and/or PD≥1 or tenosynovitis) compared with 17% (4/23) of asymptomatic patients. Among patients with inflammatory symptoms, 27% (24/88) have no joint swelling, but have MSUS-detected inflammation, while 35% (31/88) have no clinical or MSUS-detected inflammation [7].

- Patients with SLE experiencing musculoskeletal pain can have MSUS-detected synovitis without swelling (subclinical disease activity) [8].
- MSUS studies of patients with SLE demonstrate that tenosynovitis (an example is given in Figure A+B) and peri-extensor tendon inflammation (tendinitis) are the predominant features (collectively affecting 93% of patients) [9]. Tendon involvement is predominantly localized to the fourth compartment of the wrist extensor, the wrist common flexor and the third finger flexor tendon [9]. Tenosynovitis/tendinitis are more frequent in the SLE versus RA group, particularly in the wrists (73% versus 40%, p=0.037) [9].
- Similar to MRI studies, MSUS studies show a higher-than-expected presence of bone erosions in patients with SLE [6].
- Enthesitis is clearly demonstrated in patients with SLE by MSUS and PD signal, mainly at the distal insertion of the patellar tendon, calcaneal insertion of the Achilles tendon and the proximal enthesis of the patellar tendon [10].

Main challenges and Main unmet needs

- Subclinical findings such as synovitis, tenosynovitis/tendinitis and erosions (and enthesitis) are common in SLE, but their contribution for early diagnostic in SLE is limited and needs to be further delineated
- The added value of inflammatory findings detected by MRI and MSUS – next to clinical examination and immune monitoring – remains to be established for therapeutic monitoring in SLE

Perspectives

- To directly compare MRI and MSUS findings (synovitis, tenosynovitis/tendinitis, enthesitis erosions) in SLE and different SLE disease stages (early vs. late) or forms (non-deforming non-erosive arthritis vs. Jaccoud arthropathy vs. 'Rhupus')
- To assess the potential of MRI and MSUS in early SLE, incl. their differential and / or combined value
- The potential of MRI and MSUS findings in predicting disease outcome (erosive vs. non-erosive) or function (i.e. captures by HAQ, SF-36) remains to be delineated
- In comparison to MSUS and MRI, other upcoming sensitive imaging methods (e.g., fluorescence optical imaging, PET-CT, PET-MRI) require robust validation to reliably detect inflammatory changes in SLE

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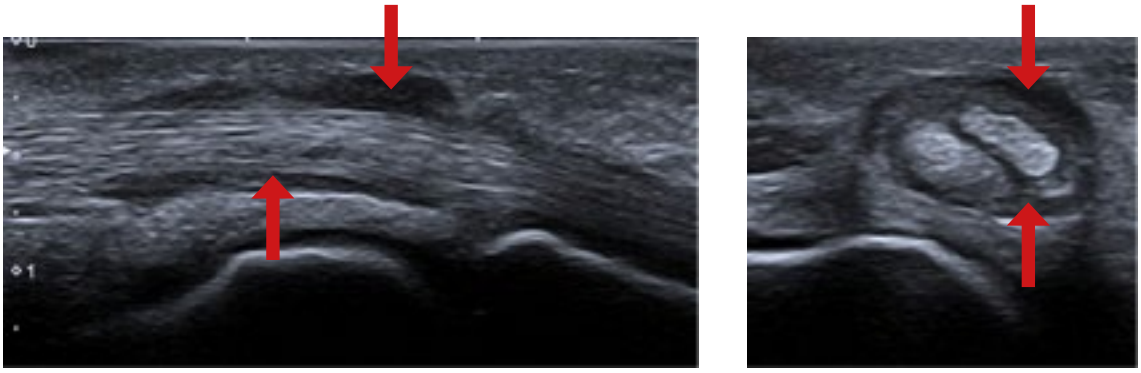

Figure A+B: Musculoskeletal ultrasound images in greyscale presenting tenosynovitis (marked by arrows) of the 2nd finger flexor tendon in the longitudinal (A) and transverse (B) view in a patient with SLE.

Management of lupus nephritis

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Context

According to current guidelines, treatment of LN should start by an induction therapy with intravenous (IV) pulse methylprednisolone followed by oral steroids in combination with either Euro-Lupus low-dose IV cyclophosphamide (500mg q2 weeks x 6) or mycophenolate mofetil (MMF) (2-3g/day). Response, ideally remission, should be maintained by MMF (1-2g/day), azathioprine (AZA) (1-2mg/day) or calcineurin inhibitors (if MMF or AZA is not tolerated) [1]. These widely followed recommendations should not disguise that current treatment regimens achieve disappointing results, with only 25-30% of LN patients with complete renal remission (CRR) after 6 months of induction treatment and up to 10% reaching end stage kidney disease (ESKD) after 10 years [2]. The need for more efficacious approaches justified many clinical trials with targeted therapies (including rituximab), which – alas – failed to reach their primary endpoint. Last year (2021) has been extremely successful for lupus nephritis (LN) clinical research, with two molecules having obtained approval from the medical agencies, belimumab and voclosporin, and others likely in the pipeline.

Key findings

- Belimumab (BEL) is an anti-BLyS monoclonal antibody used in non-renal lupus for more than 10 years. A large phase 3 trial (BLISS-LN) performed in LN patients demonstrated that the combination of BEL (10mg/kg/month) and MMF induced significantly more complete renal responses (CRR) at 2 years compared to MMF alone [30% in the BEL/MMF group versus 20% in the placebo (PBO)/MMF group] [3]. In a post hoc analysis, significantly less patients (3.6% in the BEL/MMF group compared to 11.2% in the PBO/MMF group) experienced a sustained 30% decrease of the estimated glomerular filtration rate (eGFR), which is a validated surrogate of end stage kidney disease (ESKD) progression [4].
- Voclosporin, a calcineurin inhibitor with a better toxicity profile compared to cyclosporin A, was tested in LN patients in combination with MMF in a phase 3 trial (AURORA 1). Significanlty more CRR were observed at 12 months in the VOC/MMF arm (41%) compared to the PBO/MMF arm (23%) [5]. In the 2-year extension study (AURORA 2), the benefit of VOC was maintained in terms of proteinuria, without decrease of eGFR over time.
- Other drugs are currently under investigation in phase 3 LN trials, such as obinutuzumab (OBI; anti-CD20 monoclonal) and anifrolumab (ANI; anti-IFNAR), after promising results in the phase 2 OBI trial (NOBILITY) [6] and the phase 2 ANI trial (TULIP-LN) [7].

Main challenges

While the data summarized supra will likely prompt a paradigm shift in the treatment of LN by suggesting a switch from sequential towards combination therapy with BEL or VOC (and possibly OBI or ANI), many questions remain on the research agenda:

- Should combination therapy be prescribed in all LN cases as initial treatment (as suggested by the aforementionned phase 3 trials) or used in patients failing to achieve a sufficient early response to standard of care?
- Will a higher rate of CRR with combination therapy translate in less chronic kidney disease (CKD) and ESKD in the long term?
- How long should the new drugs be prescibed?
- Will we be able to predict which patients will respond to BEL, VOC, OBI or ANI?
- What are the consequences of long-term use of VOC on kidney function and renal histopathology on repeat biopsy?
- Can we avoid oral steroid therapy through combination therapy?

Main unmet needs

While results of recent LN trials raise encouraging expectations for a better future for LN patients, there is still room for improvement, since, at best, only 41% achieve CRR with current combination therapies. Steroids, although used in much lower dose in recent trials, are still the elephant in the room, causing major side-effects. In this respect, the results of complement inhibition (e. g. with C5aR antagonists) in renal vasculitides, demonstrating surprising results without steroids, obviously raise hopes in yet another complement-mediated renal disease.

Perspectives

I have a dream! In a decade from now, several (not only two) drugs will be available that increase the CRR rate and lower CKD and ESKD rates in LN, with a minimal steroid regimen on board. This sketch is already at work for patients suffering from rheumatoid arthritis (RA). While would this not be achievable in LN, a much more severe systemic condition with a huge personal and societal disease burden? Would this dream become reality, we would face another problem (exactly as in RA): how to choose the best drug for a given patient, without proceeding – as we do today – with a rather naive trial and error approach? In a nutshell, the response will most likely be found at the tissue level, using precise medicine tools, either on the initial biopsy or on a per protocol repeat biopsy performed after one year, the value of the latter being currently tested in an international study entitled ReBioLup (www.rebiolup.com).

On yet another note, lupologists should pay attention to the results of a recent trial performed in CKD patients with dapagliflozin (DAPA), a SGLT-2 inhibitor [8]. In the DAPA-CKD trial, patients with an eGFR between 25 and 75 ml/min/1.73m2 BSA and albuminuria were treated with DAPA (10mg/day) or PBO. Most patients (67%) suffered from diabetes

mellitus. LN and vasculitis patients were excluded but patients with other glomerular diseases, such as IgA nephropathy, were included. The primary endpoint of the trial was a sustained decline in the eGFR of at least 50%, ESKD or death from renal or cardiovascular causes. The trial was stopped after 32 months when an intermediate analysis showed a 34% reduction of achievement the primary outcome in the DAPA group. The mode of action of SGLT-2 inhibitors is complex and only partly understood. In chronic glomerular diseases, the unaffected nephrons suffer from hyperfiltration, which increases sodium reabsorption in the proximal tubule, thereby decreasing sodium levels in the distal tubules and the macula densa. This leads to further vasodilation of the afferent arteriole through the tubuloglomerular feedback (vicious circle). By blocking sodium (and glucose) reabsorption in the proximal tubule and increasing sodium content in the distal tubule and in the macula densa, SGLT-2 inhibitors induce afferent arteriole vasoconstriction, reduce hyperfiltration and restore the tubuloglomerular feedback. Our educated guess is that SGLT-2 inhibitors will be a major breakthrough in all glomerular diseases, like RAS inhibitors were 30 years ago.

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Neuropsychiatric & psychological aspects of SLE

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Context

Neuropsychiatric manifestations in SLE (NP events) are a variety of central and peripheral neurological and psychiatric manifestations that accounts to significant morbidity and mortality, although its global burden is unknown. The pathways to NPSLE are postulated to be immune-mediated, thrombotic or both, but clinically validated biomarkers are scarce. The “gold standard” for NPSLE diagnosis is the expert multidisciplinary approach in experienced centres, even though, in clinical practice patients are commonly over immunosupressed. Treatment recommendations are generic for NPSLE syndromes, stratified only by presumed physiopathological clinical attribution. NP manifestations as mild cognitive difficulties, mood disorders, anxiety and headaches are common in the general population and frequently not attributed to SLE, despite recent data in favour of contributing neuroinflammatory pathways. Global burden on quality of life related to both “major” and “minor” manifestations, should drive us to address the many unmet needs in NP and psychological aspects of SLE.

Key findings

None of NP syndromes that occur in SLE have clinical, laboratory or imaging features that are specific of SLE, albeit the pathological insights (in animal models and humans) have contributed to a better understanding.

- **Clinical manifestations and Definition of NPSLE**. The 1999 ACR NPSLE syndromes case definition helped to better understand its pathophysiology and epidemiological

distribution. Its prevalence is highly variable (2.2 to 94.7%) mainly due to different attribution criteria to SLE pathophysiology itself. NP events were classified as involving central, peripheral, or autonomous nervous system, and local or diffuse. These would presumably have more vascular- (focal) or inflammatory- (diffuse) mediated mechanisms.

- **Physiopathology of NPSLE**. No single dysfunction accounts for all NP symptoms. There are two main accepted and complementary pathogenic pathways: a vascular/ischaemic pathway involving large and small blood vessels, mediated by antiphospholipid antibodies (aPL), immune complexes and intravascular thrombosis; and a neuroinflammatory pathway with complement activation, increased permeability of the blood–brain barrier (BBB), intrathecal migration of neuronal autoantibodies, local production of immune complexes and pro-inflammatory cytokines and other inflammatory mediators.
- **Serological, Cerebrospinal fluid and Imaging biomarkers**. Many promising biomarkers from blood, cerebrospinal fluid (CSF) and neuroimaging have been studied but only few are validated for clinical use for diagnosis, response to treatment or prognosis.
  - only anti-neuronal antibodies (mainly, anti-NR2 anti-N-methyl-D-aspartate receptor – NMDAR antibodies), lupus anticoagulant (LAC), anti-ribosomal P and IL-6 have been validated but only LAC and IL-6 are clinically useful for more widely clinical use.
  - for next future clinical use, serum IL-6 has been studied in monitoring NP activity and depression in SLE patients and, CSF osteopontin in treatment response monitoring.
  - Conventional MRI (cMRI) is the current neuroimaging gold standard for the assessment of patients with NPSLE, although used mainly for exclusion of other diseases. There are both clinical-imagiological and pathophysiological mismatch in 40–50% of patients with SLE. Volumetric cMRI and qualitative MRI (qMRI) techniques have shown differences in other inflammatory and neurodegenerative diseases and in small studies in NP and non-NP SLE.
- **Attribution of NPSLE**. Several attribution models have been proposed to distinguish which NP events are physiopathologically linked to SLE, but they still lack high enough specificity to be widely used compared to the “gold standard”: the expert multidisciplinary approach; close follow-up and reassessment, in experienced centres. NP events strictly attributed to SLE (immune-mediated, vasculopathy or rarely both) represents one-third of all NP events in SLE patients. The small contribution of objective data and biomarkers (e.g. psychological, radiological or laboratorial nature) makes the identification of the underlying mechanism difficult and persistent diagnostic uncertainty remains.
  - these models are useful to support NPSLE diagnosis in routine clinical practice (positive and negative predictive values are both in the range 70-85%), especially for physicians and centres with less experience. The “favouring” criteria for attribution to a primary NP event, highlights the temporal relationship to SLE diagnosis or flare, and the “unfavouring” criteria, altogether identifies mainly the most urgent, severe, highly disabling syndromes (seizures, cerebrovascular accidents, psychosis, acute confusional syndromes, polyneuropathy, severe cognition and other rarer) that need emergent treatment (immunosuppression, anticoagulation, or both). As part of this

treatment-target attribution algorithms, “non-emergent” and “minor” NP evens that are highly prevalent in the general population, like anxiety, headaches, mild depression, mild cognitive dysfunction, and polyneuropathy without electrophysiological abnormalities are low scored and excluded as primary NPSLE, although current data on these common manifestations outside SLE, have been increasingly showing immune-mediated mechanisms underlying them.

  - Non immune comorbidities, common in SLE patients (e.g.,cerebrovascular disease in patients with hypertension, chronic kidney disease, diabetes or hyperlipidemia), treatment complications, infections, metabolic abnormalities, and adverse drug reactions should be considered to exclude a primary NPSLE attribution.

- **Cognitive dysfunction**.. is highly unknown and probably multifactorial (with non-SLE contributing factors and SLE immune-mediated and vascular mechanisms). Its definition in SLE varies considerably, resulting in different estimates. Both self-reported measures of perceived cognitive impairment and simpler screening measures that detect cognitive impairment don’t capture mild deficits. Despite the efforts to harmonize cognitive assessment in SLE, there is still low degree of conformity to the ACR neuropsychological battery, likely reflecting its poor practicality. The proposed -2sd cut-off is insensitive to mild cognitive deficits, whereas the -1.5sd cut-off is widely used to identify mild cognitive impairment in geriatrics. More lenient cut-offs (e.g., -1sd below the normative mean) can be used to detect mild cognitive impairment in the general population and can uncover subtle and potentially meaningful cognitive deficits in SLE. Though, the application of less restrictive criteria especially to large neuropsychological batteries decreases specificity. Longitudinal studies of cognitive performance have made clear that, unlike neurodegenerative diseases, there is no steady cognitive decline with time in the large majority of SLE cases.

- **Anxiety, Mood disorders and Psychosis**. Anxiety and mood disorders are the most common NP complaints in patients with SLE. Nevertheless, classification of depressive and anxiety manifestations as a comorbidity, cooccurrence, association or manifestations of the primary autoimmune dysfunction is frequently unclear.

  - They may be classified as (diagnosable) psychiatric disorder or as clusters of psychopathological symptoms. Screening and monitoring tools have been validated for SLE patients. The diagnosis must follow the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), according with the symptomatology reported by the patients and assessed through a psychiatric interview.

  - After strict exclusion of other causes, lupus psychosis is infrequent (1.9–29.8% of the SLE patients), appears early during SLE and in active phases of the disease. It is an immunologically driven psychosis with promising biomarkers. Psychotic symptoms - hallucinations, delusions and disorganized speech and thought patterns – respond to antipsychotic and immune therapeutic interventions. Interestingly some authors have detected the associated presence of depression that could explain some of the clinical characteristics presented – partial insight and response to treatment.

  - Hypothalamic-pituitary-adrenal (HPA) dysfunction in response to stress, neuroinflammation, neurotransmitter dysfunction, microvascular abnormalities and disrupted neurotrophic factors are some of the mechanisms involved in both psychiatric and immune disorders.

- **Treatment of NP events**. After attribution to immune- and/or vascular-mediated phenomena, the pragmatic treatment approach is based on expert opinion, data from observational studies and extrapolation from other more validated organ involvement knowledge. Distinguishing between ongoing activity and damage is as essential as symptomatic treatment for metabolic disturbances, infections, hypertension, seizures, psychosis, anxiety, and mood disorders, privileging pharmacological (e.g. angiotensin converting enzyme inhibitors, antidepressants) and psychotherapeutic tools with immune modulator effect. In clinical practice, NP events tend to be over attributed to SLE inflammation and over immunosuppressed.

Main challenges

In face of a NP event, physiopathology attribution to SLE is suboptimal in clinical practice, despite the use of the most recent attribution models proposed, leaving a 'grey zone' of uncertainty, even more in both the most common "minor" and the rarer manifestations. It can be exemplified by the approach of a demyelinating syndrome in a patient with SLE: neuropathological studies have not found evidence of primary demyelination, therefore antiphospholipid syndrome (APS), multiple sclerosis, neuromyelitis optica spectrum disorder (all of which can overlap with SLE) or an infection namely progressive multifocal leukoencephalopathy must be pursued. Differentiating overlap conditions, drug effects, comorbidities, and psychosocial aspects is challenging for all NP syndromes and its implications on the treatment decision process are major. In contrast with other more florid NP events, the diagnosis of psychiatric disorders, as depression, anxiety, and psychosis, are often delayed or even missed in ambulatory care settings. There is not universally use of brief simple screening tools for NP signs or symptoms during flares (from specific neurological exam to symptoms of anxiety, depression, and psychosis). Limited access to the proposed cognitive tests and the lack of adequate norms partly explains the frequent deviations to the ACR neuropsychological battery. Defining clinically meaningful change, interpreting fluctuations in cognition and its association with future damage/progression is a problem. It's still unknown when cognitive dysfunction starts and how it is going to evolve.

Main unmet needs

- Prognostic, diagnostic and monitoring biomarkers for each individual NPSLE syndrome
- Screening validated, discriminative, accurate and clinically doable tools for specific NPSLE involvement (cognition, anxiety, mood, psychosis,...), including smart technology for the care of patients; the availability of high-quality cross-sectional and longitudinal normative data for cognition assessment, with adequate adjustment to the demographic characteristics of each patient (e.g., regression-based norms), is essential. More attention should be given to the issue of adequate norms.

- Therapeutic strategies directed to specific targets of NPSLE pathophysiology (e.g. BBB maintenance, pro-inflammatory cytokines, microglia activation suppressors)
- Validated clinical practice algorithms for NPSLE approach

Perspectives

To overcome the many unmet needs in NPSLE, collaborative workgroups in Europe will be able to: determine which information is minimal to multicentric registries for prospective analysis of evolution of specific NP syndromes; define a prospective multicentric research plan for each NP syndrome and centralized data collection and analysis of overlapping findings, starting with the most promising biomarkers candidates found in small studies and mice-driven research; and treatment not only for immunosuppression and non-SLE related comorbidities but also to common symptoms (anxiety, mood disorders). It might lead to move from a NPSLE syndromic classification toward a pathophysiological/mechanistic one, with standardize terminology and definitions between the different specialties involved, health care professionals and patients - disseminating a clinical practice of excellence on the work-up for diagnosis and therapeutic strategy of NPSLE.

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Measurement of SLE disease activity

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Context

Systemic lupus erythematosus (SLE) has a complex nature, with heterogeneous clinical presentation and disease course, involving one or multiple organs at a time. Organ involvement may vary widely between patients and within the same patient over time, with fluctuating levels of disease activity. Therefore, the development of a comprehensive, accurate, reliable, user-friendly, and sensitive-to-change SLE disease activity outcome measure is a main challenge [1,2]. Furthermore, there are no accurate biomarkers to measure SLE disease activity, to predict its response to drugs and estimate patients' prognosis [1,2].

Conceptually, disease activity in SLE includes all clinical manifestations and analytical abnormalities of the disease that are due to inflammatory and immune-mediated mechanisms related to the physiopathology of SLE. Thus, disease activity may potentially be resolved with anti-inflammatory (including glucocorticoids), immunomodulatory and immunosuppressant drugs used for SLE treatment. It is of utmost importance to distinguish this construct from manifestations due to irreversible organ damage, comorbidities, adverse effects from medication, and other non-autoimmune driven clinical manifestations, including type 2 lupus manifestations, such as fatigue. All these are different constructs that can have a major impact in patients' prognosis and quality of life, but, contrarily to disease activity, are not responsive to SLE medications.

Recently updated EULAR recommendations for the management of patients with SLE state that treatment in SLE should aim at remission or low disease activity and prevention of disease activity flares in all organs. Many novel targeted drugs for SLE treatment are under research, requiring optimized primary endpoints for clinical trials. Yet, these advances have laid bare the limitations of most currently used instruments for measurement of SLE disease activity and made more urgent the development of more refined tools with improved performance.

Key objectives and measurement properties

There are several key objectives that require measurement of SLE disease activity. The main objectives can be different depending on the context of use, such as the overall characterization of patient groups in observation studies, the discrimination of drug efficacy in clinical trials, or the assessment of individual patients over longitudinal follow-up in daily clinical practice. Notably, an instrument may demonstrate validity and adequate measurement properties for application in one of these contexts, but not in the others. Thus, it is essential to assess each instrument regarding the right content and measurement performance for the intended target population and objectives of application [3].

- **Daily clinical practice**. The key objectives of measuring SLE disease activity in the clinical setting are to assess individual patients, regarding the severity of ongoing disease

activity, to guide management decisions, and in longitudinal follow-up to quantify the efficacy of medications, identify attainment of treatment targets and occurrence of new flares of disease activity.

To fulfill these objectives, the instrument must have adequate measurement properties, corresponding to several types of validity. It should include the relevant disease activity features in all organ systems potentially involved by SLE (i.e., content and face validity). It should measure the activity of these manifestations with accuracy and precision, providing a numerical score of global disease activity that is clinically meaningful (i.e., construct validity). The instrument must be practical to use routinely in the clinical setting, easily accessible and quick to apply and interpret (i.e., feasible). The scores obtained with the instrument should allow to discriminate the disease activity according to categories of severity and to define attainment of treatment targets (i.e., discrimination). Longitudinal changes in these scores should have defined clinically meaningful thresholds of change, including for improvement and worsening (flare) of disease activity (i.e., responsiveness). The scores of disease activity and its longitudinal changes should have predictive value for other outcomes, such as damage accrual and patient-reported quality of life (i.e., criterion validity). The scores should present stability in situations of no change (i.e., test-retest reliability).

- **Observational clinical studies**. The key objective in observational studies is to characterize groups of participants, not individual patients, for epidemiological and prognostic study aims.

  In this context, the measurement instrument can be designed to identify the median characteristics of disease activity in larger populations, overlooking the less common manifestations (e.g., gastrointestinal, and cardiopulmonary SLE involvement, or hemolytic anemia). Likewise, activity features can be assessed just as present vs. absent, regardless of its varying severity, if the weight attributed to each manifestation is representative of the mean severity in the typical patient (e.g., most cases of thrombocytopenia in SLE are mild, despite it is severe in some patients). An instrument with such measurement properties maximizes its feasibility, especially adequate for the context of observational studies with large populations, as it will be quick and easy to assess, and more detailed information may not be available. However, there is a trade-off, as this is at the cost of lower accuracy, precision, and responsiveness.

- **Clinical trials**. The key objectives of measuring SLE disease activity in clinical trials is to compare efficacy between the study drug and placebo. This can be achieved by applying a set of criteria for defining a 'responder' (i.e., achieving on longitudinal follow-up the threshold for a clinical improvement) that is dichotomous – responder vs. non-responder. This allows to compare the proportion of responders between the treatment and placebo arms of the clinical trials. A different option would be to assess longitudinally a continuous measure of SLE disease activity and compare the changes in the numerical scores from baseline to end of study between treatment and placebo groups. This approach may allow to assess the treatment effect size more accurately. An additional objective is to compare efficacy in terms of prevention of SLE disease activity flares between treatment and placebo groups.

To fulfil these objectives in the setting of clinical trials, responsiveness is a measurement property of the disease activity instrument that should be optimal. As SLE is a multisystemic disease, the instrument should give a comprehensive longitudinal assessment in all organ systems, to provide a balanced measure of change in such a way that patients with an improvement in some organs offset by concomitant worsening in other organs are not inappropriately considered responders. Other validity properties of the instruments are also important in the clinical trial setting. However, aiming to maximize these properties, more complex composite indexes are currently applied, at a major cost of reduced feasibility [4].

Main challenges

Several validated instruments for measurement of SLE disease activity are available; however, a main challenge is that none is currently recognized as a 'gold-standard'. Among these, the most frequently used in daily clinical practice and observational clinical studies are the SLE Disease Activity Index (SLEDAI) (with the SELENA-SLEDAI and SLEDAI-2K versions) and the Physician Global Assessment (PGA); in clinical trials, the British Isles Assessment Group (BILAG) index (with the BILAG-2004 updated version) is also assessed, in addition to the SLEDAI and PGA [5].

The SLEDAI is a 24-item instrument that is simple and quick to score, thus presents good feasibility, but does not include several important and potentially severe SLE manifestations and its responsiveness to change is limited [5,6]. Thus, its performance is sufficient for observational studies, but not good enough to guide management of individual patients in daily clinical practice. The PGA presents good feasibility and responsiveness; however, due to a lack of standardization has a limited reliability [7]. Its use is included in current EULAR management recommendations. The BILAG-2004 is a comprehensive instrument with 101 disease activity items; however, its high administrative burden limits feasibility in clinical practice. A new tool, the Easy-BILAG, facilitates its scoring [8]. The SLE Disease Activity Score (SLE-DAS), a 17-item instrument with continuous measurement properties was recently developed and validated [6,9,10]. It is feasible in clinical practice, being practical to score with its online calculator (http://sle-das.eu/). It presents very good responsiveness and discrimination of categories of active disease and treatment targets; thus, it may be appropriate to assess individual patients and guiding treatment in daily clinical practice.

Recognizing the limitations of SLEDAI, BILAG, and PGA, composite responder indexes were developed (i.e., SLE Responder Index [SRI] and BILAG-Based Composite Lupus Assessment [BICLA]), both including these three instruments. The SRI and BICLA are used as primary outcome measure in SLE clinical trials. However, these responder indexes do not improve responsiveness, which is a main challenge for clinical trials. Indeed, the determinant of sensitivity to improvement in SRI is the SLEDAI, while for the BICLA is the BILAG. Shortfalls in responsiveness were found equally for both indexes [4]. Importantly, the SRI and BICLA do not estimate treatment effect size, are not feasible in the clinical practice setting, and not appropriate to identify flares or attainment of treatment targets.

Main unmet needs

- **For daily clinical practice**: definition of a 'gold-standard' instrument to measure SLE disease activity with high validity, reliability, responsiveness to change and feasibility, to

facilitate the management of patients with SLE and guiding treatment decisions.

- **For clinical trials**: definition of a 'gold-standard' instrument to measure SLE disease activity with high validity, reliability, responsiveness to change and feasibility, to:
  - Apply as primary outcome measure to identify responders
  - Assess the treatment effect size of new drugs
  - Identify flares of disease activity
  - Identify attainment of treatment target states
  - The same instrument should be able to fulfill all these objectives in any settings, to allow application and ensure validity of results of clinical studies in the daily clinical practice.

Perspectives

Recent advances in treat-to-target strategy for management of SLE patients and the current challenges to improve the design of SLE clinical trials have made clear the critical need for accurate measurement of SLE disease activity in daily clinical practice and trials, while clearly exposing the major limitations of most currently available instruments. The prevailing approach to fill these gaps is to add other items to existing instruments. Unfortunately, this resulted in an assortment of more complex and less feasible tools, for defining treatment targets, responders, or flares, while their performance remains disappointing. Ongoing research holds promise for defining an optimized instrument fulfilling the key objectives for measuring SLE disease activity.

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How to define and how to manage LDA and remission in SLE

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Context

According to current guidelines, treatment of SLE should aim at achieving remission or, when remission cannot be achieved, at the lowest level of disease activity [1]. In the last few years, a wide number of definitions of remission were proposed, and compelling data proved that remission, whatever definition is used, is associated with better outcomes in terms of damage, survival, and quality of life.[2-4] Finally, in 2021 a shared definition of remission has emerged, which is based on SLEDAI-2K, PGA, and therapeutic items.[5] On the other hand, the concept of low disease activity (LDA) has only recently been applied to lupus, being the LLDAS (Lupus Low Disease Activity State) by the Asia-Pacific Lupus Collaboration the first definition of LDA for SLE. So far, a great amount of data has shown that LLDAS is associated with better short-term outcomes. [6-8]. Other attempts to define LDA are ongoing, including the promising SLE-DAS based definition [9]. Now what should be addressed is how to manage patients in remission and in LDA.

Key findings

- The DORIS task force defined remission as the absence of clinical disease activity (clinical SLEDAI-2K=0 and PGA <0.5) in patients treated with stable doses of immunosuppressants, antimalarials, and a current prednisone dose ≤ 5 mg daily.[5]
- The most used definition of LDA is the LLDAS, defined as: 1, SLEDAI-2K≤4, with no activity in major organ systems (renal, central nervous system (CNS), cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; 2, no new lupus disease activity compared with the previous assessment; 3, a SELENA-SLEDAI PGA≤1; 4, a current prednisone dose ≤7.5 mg daily; and 5, well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.[6]
- Long-term glucocorticoids therapy is associated with side-effects and complications [2] and, thus, in remitted patients an attempt to decrease and/or withdrawal prednisone should be done.
- Even immunosuppressants use is associated with damage accrual [10] and recent evidences suggest that the withdrawal of immunosuppressants may be safely attempted in selected patients, i.e. those in prolonged remission (>3 years) and who were taking hydroxychloroquine (HCQ). [11, 12]
- According to expert opinion, remitted patients should be monitored for signs and symptoms of disease recrudescence, maintaining a regular follow-up with a 4-6-month interval.
- When remission can not be achieved (i.e., residual disease activity or need for medium glucocorticoid doses), LDA represents a suitable outcome.

Main challenges

Some questions remain on the research agenda:

- Can we stop glucocorticoids in SLE after remission achievement? Published data are contradictory. [11, 13-15]
- Should we stop glucocorticoids before immunosuppressive therapy or viceversa in remitted patients? Both approaches are reported in the literature, and no definite conclusions can be drawn.
- What is the true role of HCQ in maintaining remission? Studies powered to evaluate the protective effect of HCQ in remitted patients are lacking.
- How long can we keep remitted SLE patients on antimalarials? HCQ is a milestone in the management of SLE patients, but long-term use has been associated with ocular toxicity, especially in older patients with renal impairment.[16]
- Do patients with previous renal involvement deserve a different management during remission?
- Which are the clinical features of a patient in LDA? Although LLDAS represents a succesful first definition of LDA in SLE, a description of what LDA looks like in clinical practice remains elusive. Indeed, since most SLE patients show a relapsing-remitting activity pattern, it might be that LDA represents a transitory state between remission and active disease in most cases.
- How to manage patients in LDA still remains a matter of dicussion
- How often should we evaluate patients in LDA? Do patients in LDA due to high-glucocorticoid threshold deserve a different management compared with patients in LDA due to residual disease activity?

Main unmet needs

We still have some unmet needs, in particular we do not know which are the baseline clinical, serological, or therapeutic predictors of a state of durable remission; in this regard, it would be of utmost importance to identify biomarkers able to predict the course of the disease in the upcoming years since SLE diagnosis. In addition, we still have to completely understand the kinetics and predictors of flares after remission achievement: why do some patients in prolonged remission flare at certain point in their life? In addition, why do some patients flare after the withdrawal of very low maintenance dose of glucocorticoids? Do really 5 mg of prednisone have immunosuppressive capability able to prevent disease flares? We are probably missing something that can distinguish between patients in “true” remission from those in a transient state of quiescent disease. Moreover, we are probably ignoring some trigger of disease reactivation.

On the other hand, which is the best management of patients in LDA is still a matter of debate: are they active patients, who as such need a careful monitoring, i.e. every 3 months, or are they patients in a state very close to remission, so than they can be followed-up less strictly? And also, is persistent low disease activity a sufficient/adequate target in the long

term, or would it bring along some amount of damage related to corticosteroid use and creeping disease activity?

Perspectives

SLE is a multifaceted disease, with many different clinical phenotypes. The current strong effort for identifying biomarkers of response to therapy in the -omic era would hopefully allow us to better treat each patient, through a personalized approach. In particular, it would be of primary importance to define which drug/combination of drugs has the highest probability to induce remission in a single patient yet avoiding overtreatment, as the earlier the remission, the lower the burden of the disease and damage accrual,. In this perspective, the number of ongoing clinical trials of biological agents in SLE would pave the way to a more diversified and targeted therapeutic approach, based on patient's -omics profile.[17]

In the end, by ten to fifteen years, it will be probably possible to treat SLE as Rheumatoid Arthritis, with different biological or targeted synthetic DMARDs, aiming at clinical remission by blocking different pathogenetic drivers of the disease.

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Cardiovascular disease in systemic lupus erythematosus

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Context

Cardiovascular disease (CVD) is currently recognized as a main cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE) [1, 2]. In contrast to the general population, women are affected more frequently and earlier, usually in the premenopausal period. Patients with SLE have 2 to 8-fold increased risk of stroke compared to non-SLE controls and at least a 10-fold risk of ischemic heart disease. Microvascular involvement is also present and is often asymptomatic.

CVD pathogenesis in SLE is complex. In addition to classic CVD risk factors (e.g. hypertension, obesity, smoking, hyperlipidemia or diabetes), a plethora of disease-related factors are also involved including demographic factors, disease activity, disease damage, medications and especially the use of glucocorticoids, and a prothrombotic state related with the presence of antiphospholipid antibodies [3].

Key findings

- Early identification and management of CVD risk factors is crucial to reduce the prevalence of cardiovascular disease in SLE
- Independently of the role of the traditional risk factors, disease-related factors have an important impact on CVD risk in SLE
- Generic CVD risk prediction tools or modified tools for SLE have been used to assess CVD risk
- Poor CVD risk control may be impacted by 1) low awareness of CVD risk among patients and physicians caring for patients with SLE; 2) poor implementation of measures for the management of CVD risk factors.

Main challenges

Prevalence/incidence. Over the past 20 years, a steady decline in the incidence of acute coronary syndromes and stroke has been observed in the general population. However, a US population-based study using nationwide data found increased age-adjusted rates of hospitalizations for myocardial infarction and stroke between 1996 and 2012 in both women and men with SLE vs the general population, and a 13-times higher rates of hospitalizations in SLE vs non-SLE populations [4].

Risk assessment. Until mechanisms underlying CVD risk in SLE are fully elucidated, optimizing screening and modification of known risk factors are essential. Limitations in

traditional CVD risk factor screening (blood pressure, smoking, lipids, body mass index, diabetes) and counseling about their prevention and management in routine practice have been documented by observational and population-based studies. However, it is unclear whether control of these risk factors alone is sufficient to prevent CVD events, or if interventions targeting SLE-specific risk are equally or more important. Control of inflammation, minimization of corticosteroid exposure, or prophylactic measures against thrombosis in patients with positive antiphospholipid antibodies can help to reduce the burden of CVD in SLE.

For the assessment of CVD risk, risk prediction models used in the general population such as the Framingham score and the heart SCORE have been also applied in patients with SLE. Evidence has shown that Framingham score underestimates CVD risk in SLE, while limited data are available about the performance of SCORE. Disease-specific prediction tools are needed (although this is a very difficult task), incorporating the disease-related CVD risk factors.

Surrogate vascular markers have also an important role in CVD risk stratification. A 2-3 higher risk of subclinical atherosclerosis, an early indicator of cardiovascular disease, has been demonstrated by vascular ultrasound studies [5]. The presence of ultrasound-detected carotid plaques has been recommended by the European Society of Cardiology as a CVD risk modifier in the general population. Measures of arterial stiffness such as the pulse wave velocity, and markers of endothelial dysfunction as the flow-mediated dilation, have been also shown by some studies to be more impaired in SLE than in the general population. Coronary artery calcium has also been examined as a potential risk modifier.

CVD risk management. EULAR has recently published recommendations for cardiovascular risk management in Rheumatic and Musculoskeletal Diseases, including Systemic Lupus Erythematosus and Antiphospholipid Syndrome [6]. The main challenge for the development of these recommendations was the limited number of studies addressing some of the research questions and the small number of randomized controlled studies.

Aspirin use in SLE has been associated with lower risk of CVD events in SLE in observational studies and especially in patients with positive antiphospholipid antibodies. The corresponding statement from the 2019 EULAR recommendations for SLE management was endorsed, reporting that SLE patients may be candidates for preventative strategies as in the general population, including low-dose aspirin, based on their individual cardiovascular risk profile [7].

There are only a few RCTs examining the role of statins on primary CVD prevention in SLE. Two studies found that low-dose atorvastatin had no effect on the progression of atherosclerosis. Another study found that low dose rosuvastatin led to a reduction of hsCRP levels. Lipid treatment was suggested to follow recommendations used in the general population.

Regarding blood pressure management, a blood pressure target of <130/80 mm Hg should be considered. For patients with lupus nephritis with urine protein-to-creatinine ratio >500 mg/g.

Or arterial hypertension, the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers is recommended.

Use of hydroxychloroquine has been associated with a lower risk of CVD events in several longitudinal SLE studies but RCTs examining CVD events specifically as outcomes are lacking. Treatment with hydroxychloroquine has been recommended by the EULAR for all patients with SLE (unless contraindicated) and may also reduce the risk of cardiovascular events. Glucocorticoid exposure should be minimized to the lowest possible dose and duration, while no specific immunosuppressive medication is recommended to reduce the risk of CVD events.

Main unmet needs

- Increase of awareness of CVD risk among physicians and SLE patients
- Validation of existing generic and modified CVR prediction tools
- Development of SLE-specific CVD risk prediction tools
- Assessment of the role of older and new immunoregulatory agents on CVD risk
- Minimization of glucocorticoid exposure to the lowest effective dose and for the shortest duration
- Educational campaigns for promoting CVD risk management

Perspectives

Both patients and clinicians should be aware of the increased cardiovascular risk and the required strategies for its minimization. A multidisciplinary approach for CVD risk screening and treatment is needed to improve cardiovascular disease prevention. All individuals with SLE should get regular CVD risk factor monitoring and a strict control of modifiable factors, including smoking cessation and management of blood pressure, lipids and glucose. Patient education, treatment adherence to achieve low disease activity, and lifestyle modifications are also important for CVD management in these patients.

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Pregnancy: SLE before, during and after pregnancy

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Context

Nowadays, most of the young women affected by Systemic Lupus Erythematosus (SLE) can carry out a good pregnancy outcome thanks to the improvement in treatment and management and the consequent reduction in morbidity and mortality.

Key findings

Principal international scientific guidelines agree on some points that every clinician should keep in mind while approaching a young woman with SLE [1, 2].

- The recent diagnosis of a systemic autoimmune condition and of an active disease are prognostic bad factor for the mother and the baby and therefore the patients should be encouraged to postpone pregnancy. SLE activity, disease flares at conception or in the last 6-12 months prior to pregnancy may increase the risk for maternal disease flares during pregnancy and puerperium and for fetal morbidity (in particular pregnancy loss, intrauterine growth restriction - IUGR, preterm delivery). Also, a history of lupus nephritis or active renal disease at conception is a strong predictor for the recurrence of renal flare during pregnancy and for a poor fetal outcome. In addition, active serology at conception (low serum C3 and C4 complement fractions, positive anti-dsDNA) increases the risk for maternal complication, in particular flares during pregnancy, and may lead to pregnancy loss.
- Another important finding is the increased knowledge about the safe use of antirheumatic drugs in pregnancy. Nowadays clinicians have multiple choices of medications that allow maternal disease control without harming the fetus [3], as Hydroxycloroquine (HCQ) and Cloroquine (CQ), conventionally used in patients with SLE. HCQ in particular seemed also to show a protective role for pregnancy outcome itself and discontinuation of HCQ during pregnancy could result in a maternal flare and consequently in a possible difficult situation for the mother and the fetus. On the other hand, some immunosuppressive drugs are contraindicated during pregnancy due to their mutagenic and teratogenic effects. It is the case of Methotrexate (MTX) and Cyclophosphamide (CYC) that could be used for some clinical manifestations of SLE and that should be discontinued three months before conception. In addition, Mycophenolate mofetil (MMF) often used in SLE patients could be associated with an increased risk of congenital anomalies (especially facial dysmorphology) and should be discontinued at least 6 weeks before conception. To note, other immunosuppressive drugs are usually used during pregnancy due to the absence of negative fetal effects, such as azathioprine (AZA), cyclosporine and tacrolimus. Two biological agents could be used in patients with SLE. Rituximab, an anti-CD20 monoclonal antibody, required at least 6-12 months after infusion for the research of a pregnancy due to possibly immunodepression of the fetus. Belimumab

(a fully humanized IgG1g monoclonal antibody directed against soluble B lymphocyte stimulator) has not been associated with an increased rate of fetal abnormalities or adverse pregnancy outcome, however, data of the literature are not sufficient to clearly define its safety during pregnancy. Expert opinion is to stop the therapy at pregnancy positive test. Counselling on therapy before pregnancy is mandatory for every young SLE patients who desire a pregnancy in order to discuss with the clinician about the possibility to continue or not the ongoing treatment.

- Particular attention and strict monitoring should be dedicated to SLE women with specific antibodies profile: patients with antiphospholipid antibodies positivity (testing all the three available tests: antiBeta2Glycoprotein I IgG/IgM, anticardiolipin antibodies IgG/IgM, Lupus Anticoagulant) or Antiphospholipid syndrome, who are at higher risk for maternal and fetal complications, and patients with anti-Ro/SSA and/or anti-La/SSB antibodies, because of the risk of neonatal lupus including congenital heart block. aPL are well known risk factor for adverse pregnancy outcome, in particular in presence of a high-risk profile (lupus anticoagulant positivity, triple aPL positivity, moderate to high titre aPL, IgG isotype). Main obstetrical complications are described as spontaneous abortions (<10 weeks of gestation), fetal loss (≥10 weeks of gestation), preterm delivery before 37 weeks of gestation, preeclampsia, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet). Therapeutic approach, however, has largely improved the maternal and neonatal outcome. The treatment, that is modulated on the risk stratification, usually includes low-dose aspirin and low molecular weight heparin in combination. Maternal anti-Ro/SSA and/or La/SSB can cross the placenta during the second trimester and could affect the baby with different degrees of severity, ranging from mild cutaneous manifestations to cardiac manifestations, in particular conduction abnormalities (first-, second-, third-degree congenital heart block (CHB)). This complication is less common than other manifestations and it affects approximately 2% of exposed offspring with a recurrence rate estimated between 12% and 17%. By the way, the livebirth rate in affected pregnancies ranges from 84% to 71% as supported by several registries [4].

Main challenges

During SLE pregnancy, two are the main concerns of the future mothers: the effects of pregnancy on their diseases and the impact of SLE itself on obstetric/foetal outcome [1,2,5]. In fact, despite the improvement of pregnancy outcomes, patients with SLE still shows worse obstetric and neonatal outcomes than the general obstetrical populations [6]. The most recent studies observed a pregnancy loss rate of 10-25%: unplanned pregnancy, uncontrolled disease activity with active serology and active lupus nephritis are described as the most important risk factors. Also, preterm birth, defined as delivery before 37 weeks gestation, remains increased in SLE patients, with a prevalence that vary between 25-40%. Preterm birth is usually spontaneous, mainly due to the premature rupture of membranes, but it can be induced in the case of onset of fetal distress or hypertensive disorders as pre-eclampsia to protect the health of the mother and/or of the baby. Several risk factors for preterm delivery have been identified, as uncontrolled disease activity prior to and during

pregnancy, previous renal involvement, the use of medium-high dose of prednisone during pregnancy, or pre-existing hypertension [2].

It is worth noting that hypertensive complications, including pregnancy-induced hypertension, pre-eclampsia/eclampsia and HELLP are one of the main concerns for SLE pregnant patients, not only because they can cause pregnancy complications but also because they represent a risk factor for the mother for subsequent cardiovascular disorders as chronic hypertension [7]. Due to all these causes, the occurrence of babies with low weight or small for gestational age are common in SLE pregnancies, ranging from 6 to 35%. Obviously, particular attention must be placed at babies with severe preterm delivery born, in particular those born before 28 weeks gestation, because they are at highest risk for both short and long-term medical complications and cognitive impairment.

The other main concern is the risk of the occurrence of disease flares during and after pregnancy. For many reasons it is difficult to quantify the incidence of such complications. First, it can be not easy to distinguish between physiological changes of pregnancy from signs or symptoms linked to SLE flares. In fact, some symptoms as fatigue, arthralgias, cutaneous manifestations commonly occur during healthy pregnancies. On the other hand, some symptoms of preeclampsia, as the onset of proteinuria, hypertension and thrombocytopenia may mimic a lupus nephritis flare. Even with some discrepancies on available clinical studies, we can estimate that about 35-70% of women with SLE may experience a disease flare during pregnancy (mainly in the second half) or during the first-year post-delivery. Disease flares are generally mild and tend to present with mucocutaneous, musculoskeletal and hematological manifestations, but also an increased risk of possible reactivation of more severe manifestations, as lupus nephritis, has been reported. Disease flares after birth are usually consistent with the manifestations occurred in the six months prior to conception and tend to be more frequent in the first few weeks, although they may develop up to one year after delivery. It is even more difficult to estimate the occurrence of flares in the post-partum because of the heterogeneous definitions of flares and differences in the follow-up after delivery evaluated in the available studies [8].

Onset of SLE during pregnancy is a rare event, and it is associated with a worse pregnancy outcome than in patients with an established disease: in the majority of the described cases, the onset occurs during the first half of the pregnancy, and renal and haematological features are the most common [9].

Main unmet needs

Despite the great improvements of maternal and fetal outcome observed in SLE pregnancy, we know several conditions that can affect maternal or neonatal outcome and that need to be carefully considered. As already mentioned, active disease up to one year before conception, shorter disease duration before conception, previous lupus nephritis (not necessarily active during conception), immunological abnormalities such as low complement levels, anti-dsDNA positivity and antiphospholipid antibodies, discontinuation of pharmacological treatments during pregnancy, history of hypertension can increase the rate of maternal and obstetric complications. Conversely, continuous therapy with hydroxychloroquine is identified as a protective factor [1,2, 10,11]. However, we still do not

have a treatment able to abrogate all the complications as those occurring to patients with lupus nephritis, even in remission and without renal insufficiency, such as hypertension, preeclampsia [12,13].

SLE patients also presents an increased risk for possible post-partum complications, like infections and thrombotic events. Even in healthy women, post-partum is considered a critical period for the onset of thrombosis, and cesarean section is one of the greatest risk factors. Patients with SLE, in particular if they have antiphospholipid antibodies, carry an additional risk for this complication [14].

Finally, it should be carefully considered that, once pregnancy is confirmed, multidisciplinary periodic visits are needed, with a frequency related to the maternal disease activity [1,2]. The so called "Pregnancy Clinic" should include besides lupus experts, also Obstetrics/Gynecologists. In fact, current standard of care in SLE pregnancy includes doppler studies of uterine arteries and umbilical arteries starting from the 20-24th week. These procedures are helpful to evaluate placental function with the aim to exclude early disfunctions that can predict fetal distress and preeclampsia. In case of presence of anti-Ro/SSA antibodies, it can be advisable to perform regular fetal echocardiograms between the 16th to the 26th week of gestation (which is the period of enhanced transplacental passage of maternal antibodies) [2].

Perspectives

Accordingly, a proper counselling should be proposed to all young patients: pregnancy is a precious moment and especially in women with SLE it is mandatory to plan it in a period of remission of the disease. A correct timing for pregnancy, together with a tight monitoring during the three trimesters and the post-partum period (to timely identify and treat possible obstetric complications or maternal disease flares), as well as the concept of multidisciplinary management, are currently milestones of the management of pregnancy in SLE patients. Counselling, an important part of an effective physician-patient communication, is sometimes an unmet need for young patients with rheumatic diseases but it is essential in order to estimate the possibility to manage both fetal and maternal problems, related to disease activity, serological profile or eventual organ involvement as contraindication to pregnancy [15].

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Infections, vaccination & SLE

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Context

Systemic lupus erythematosus (SLE) patients are more susceptible to infection and infections remain one of the top causes of mortality in SLE patient cohorts. Several disease-specific characteristics account for this increased risk as does the treatment burden necessary to control SLE. Evolving approaches to the management of SLE and to preventing, diagnosing and treating infection have the potential to change this burden. At the same time, changes in epidemiology and environmental pressures continuously create new challenges, rendering it hard to ascertain the infection risk of any specific patient. Physicians must carefully weight all these factors and work with patients towards better outcomes in infection in SLE.

Key findings

Infection is still one of the leading causes of morbidity and mortality in SLE: patients have a 2- to 6-fold increase in relative risk of infection and are 2 - 4 times more likely to be hospitalized due to infection than age- and gender-matched general population cohorts. This translates to nearly half of patients having a severe infection during the course of their disease. Some 10 to 35% of hospitalizations in SLE are due to infections, with recent evidence showing they have been increasing. Infection accounts for up to one-third of deaths in SLE, with increased preponderance classically recognized in the first five years of disease, but extending throughout the entire arch of disease, rendering infection one of the top causes of mortality in SLE.

SLE can inherently, but not inexorably, result in increased risk of infection. Disease activity, measured by SLEDAI, has been shown to be an independent risk factor for infection in SLE patients and lung involvement, specifically, seems to substantially escalate this risk. Accrual of damage, including comorbidities such as diabetes and cancer, is also associated with increased infection risk and worse outcomes. The influence of disease duration alone on this risk is not consensual, reinforcing the notion that increased risk is not inescapable. Rather the focus should be on prevention.

SLE can compromise all immune system compartments. Polymorphonuclear leucocytes, the macrophage-monocyte system and NK cells all have reduced or dysfunctional activity in SLE. Lymphopenia, also common in SLE, resulting in decreased numbers of T lymphocytes, impairs not just direct cytotoxic activity but also cytokine production such as IL-2 and IFN-ɣ. Hypocomplementemia, usually taken to herald a flare, can be both acquired and congenital (such as congenital C1q and C4 deficiency, for instance, closely linked to SLE), and adds to the immune compromise. Hypogammaglobulinemia, particularly in lupus nephritis or with

B-cell depleting therapy, could increment the risk for infection, requiring vigilance. Finally, patients with primary immune deficiencies can present with autoimmune features, often mimicking SLE. These patients are probably underdiagnosed and there is a lack of consensus on when and how they should be approached and treated.

Immunosuppression increases infection risk in SLE patients. Steroids are a major contributor, carrying an increased risk of infection at doses of at least 7,5mg/day or greater. Cyclophosphamide remains another of the greatest infection risk-inducers, although this could be mitigated, whilst retaining efficacy, by using low-dose cycles. Conventional DMARDs are generally considered to confer additional infection risk. Comparisons are limited, however, by lack of standardization on their use and definitions of infection. Infection can be a result not only of the desired direct immunosuppressive effect of drugs but also from their multiple and complex interactions.

Newly approved drugs for SLE have shown smaller rates of infection, mostly similar to placebo arms, albeit, for the most part, in relatively short follow-up periods. The safety profile of Belimumab, which accumulates the most longer term data, holds across time and although no trials directly compare them, the risk of severe infections seems lower than with DMARDs or rituximab.

It can be difficult to distinguish infection from flare in SLE even though given the potentially severe consequences it is peremptory that such a distinction be made systematically, accurately and in timely fashion. Besides classical disease activity markers, such as dsDNA antibodies and reduced complement, the erythrocyte sedimentation ration (ESR) / C-reactive protein (CRP) ratio was found to differentiate between infection and flare in SLE patients. Procalcitonin, although potentially better than CRP alone for diagnosing bacterial infection in SLE patients, still does not have an established role in patients with autoimmune diseases. Neutrophil-to-lymphocyte ratios (NLR) have shown good specificity for the diagnosis of infection in SLE and their combination with CRP increases specificity and negative predictive value further. Levels of specific cytokines and immunophenotyping profiles could potentially improve this diagnostic capability.

Microorganisms and site of infection in SLE overlap those of the general population, with a predominance of bacterial infections in the respiratory and genitourinary tracts. SLE patients are, however, not only more susceptible to infection but also to complications, with up to 5 times the incident risk of invasive pneumococcal disease, for example. Mortality due to infection in SLE occurs more frequently from generalized, invasive infections, of mixed etiology, with fungi present in a majority of cases. Specific viral pathogens are of particular relevance in SLE, because infection or complications are preventable. Human papilloma virus (HPV) de novo infection and persistence are higher in SLE, with more high-risk serotypes. It is thought that immunosuppression increases risk for cervical cancer in these patients. Varicella zoster infections are also more frequent in SLE, both compared to the general population and other autoimmune disease, and its infection rate has been increasing.
COVID-19 is the most recent disease to add to this list. Commonly used DMARDs to treat SLE do not seem to increase risk of infection or worsen outcomes, with the exception of high-dose steroids and rituximab, which result in higher hospitalization and mortality rates. Non-white

populations, those with major comorbidities and disease damage are also reported to have worse outcomes. Case series do not report a substantial increase of severe SLE flares with SARS-CoV-2, although there are cases of light/moderate flares up to 22 days from infection. Preventing infection in SLE. Hydroxychloroquine has been shown to have hugely beneficial impact in infection prevention, reducing major infection up to 16 –fold. Steroids should be used at the lowest dose and shortest duration possible, in adherence to treat-to-target strategies. Use of low-dose boluses of IV steroids can control acute disease activity, while at the same time reducing the total cumulative dose of corticosteroids. New drugs and treatment approaches for SLE have shown that they can drastically reduce the cumulative dosage of steroids and allow for quick tapers. Some schemes have even striven to do away with oral steroids altogether.

Anti-pneumococcal, anti-influenza, anti-herpetical and, more recently, anti-SARS-CoV-2 vaccination are important preventative measures against infection, morbidity and mortality in SLE patients. For currently marketed vaccines, most available data does not point to a consistent increase in clinically-relevant SLE flares, particularly in patients with stable SLE.

Infections at the base of SLE and flares. In the past decades knowledge has been accumulating on the effects of infections as triggers of SLE or SLE flares. This includes evidence from single pathogenic agents, such as Epstein-Barr virus or parvovirus B19, but also from genetics, through human endogenous retroviruses, integrated into our genome 40 million years ago, and associated with SLE and SLE activity. Newer and cheaper gene sequencing techniques, supported by improving bioinformatics capabilities, have facilitated the expansion of immunology research into ecology. Characterization of the vast amounts of bacteria in frontier territories, such as the gut, has revealed commensals to trigger autoimmunity in SLE, and dynamic changes in microbiome to be associated with disease activity in patients. As such, artificial modulation of these environments serves to show the potential benefit of continuous exploration of host pathogen interactions.

Main challenges

The pathophysiological factors leading to infection in SLE are not completely understood and are likely not the same for every patient. This reinforces the need to improve individualized risk assessment which, so far, has been hampered by a lack of standardization of infectious outcomes and of treatment regimens in the literature that prevent comparison. The paradigm is glucocorticoid prescription, highly variable among physicians and with no consensus on dosing, tapering regimens or minimum objective. It is thus unsurprising that different initiatives, in different cohorts, comparing the infectious risk of DMARDs have provided conflicting results adding to the pressure felt by physicians when deciding on treatment. This is especially true when facing a severe infection, often during a concomitant flare. The improvement of supportive therapy has given rise to increasingly difficult questions such as when and which DMARDs should be de-escalated, if they should be later reintroduced and, if so, when? In the face of these challenges prevention is key, but effective and safe preventative care such as universal hydroxychloroquine use and vaccination remain underutilized. This is compounded by access and adherence issues. In some geographies, for instance, specific cohorts of SLE patients, such as younger patients, are not eligible for certain free immunizations included

in national plans (eg. anti-pneumococal vaccination) or these are not available (eg herpes zoster).

Main unmet needs

- Prospective, multicentric, registries to allow gathering standardized real-life data on different treatment schemas, their cumulative dosage and risk of infection. This should include common progress towards a unified strategy for steroid tapering aiming to reduce infections.
- Research into the role of genetics, environmental exposures, disease activity, comorbidities and damage in modulating the infectious response. Development of robust and practical means of accounting for these ever-changing factors individually, possibly using digital health tools, for the physician and patient alike.
- Improve the recognition and characterization of patients with greater immune compromise and establish a consensual approach to work-up and follow-up, including the role of judicious use of prophylactic antibiotics for selected patients.
- Better, more specific, easily accessible and cost-effective biomarkers to distinguish flare from infection, and improve the diagnosis of life-threatening infections.
- Individualized vaccination strategies, supported by efficacy data specific to SLE, and according to clinical characteristics and ongoing treatments. Exploration of the mechanisms of (the rare) vaccine-induced flares and how to prevent them.
- Improve the dissemination and sharing of information among patients and physicians reinforcing the common objective of improved infectious outcomes in SLE.

Perspectives

To conquer infection in SLE will require a coordinated effort between patients, patient associations, physicians, researchers, health systems and governments. There have been increasing advances in fundamental and translational research, characterizing the myriad genetic and environmental pressures and modulators that interact daily with the patient's immune system and might result in disease and flare. Electronic health records and apps, bioinformatics and artificial intelligence will allow for the conception of unprecedented interaction maps (an "interactome of interactomes") in an ever increasing landscape of personalization of microorganisms and their host. This information will be applied to SLE.

COVID-19 has shown us that the society is ready and capable of supporting our patients through some of the changes required to keep them safe. These should be continuously developed. For clinicians, multicentric, international collaboration to approach new infectious risks in SLE should be maintained after COVID-19, and expanded across countries and areas of expertise.

Increased access to information will empower our patients to make the best decisions for their individual situation. Clinicians should strive to produce relevant research, allowing for standardization of prophylactic and treatment approaches with the ultimate goal of establishing and systematizing a personalized medicine.

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Glucocorticoids in SLE

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Context

Evolving practice recommends the use of the minimal efficacious glucocorticoids (GC) dosage to manage active manifestations of systemic lupus erythematosus (SLE), followed by a tapering to low doses (prednisone <7.5mg/day) as soon as it is feasible. According to current recommendations for SLE management, the use of GC pulses over oral steroids is advised for potentially severe manifestations [1], which would both minimize overall GC intake and ease subsequent GC tapering [2]. This is biologically based on the incitation of the non-genomic GC-related pathways [3] which culminate in a greater anti-inflammatory effect, thereby allowing the use of a lower starting oral GC dose [2,4].

The approach to using the lowest effective GC dosage has emerged in the last two decades owing to the knowledge of GC contribution to accruing organ damag [5,6] as well as to data showing that lower GC dosages are as protective as higher doses, yet minimizing drug-related side effects [7]. However, no high-level evidence is available on long-term effects of low versus higher GC schemes and no universal schedule for a safe GC tapering has been released. Moreover, the only clinical trial aimed at attempting GC withdrawal in a SLE cohort documented an increased rate of flares in patients deprived of even low dose GC [8], and the first meta-analyses summarizing available data on different GC regimens did not show a clear superiority of low-dose approaches [9], confirming still a relevant variability in GC management. On the other hand, safe GC tapering and withdrawal has been reported across small cohorts of SLE patients having achieved a durable clinical remission before tapering [10,11], and the use of lower-doses of GC pulses followed by a fast oral GC tapering was applied in successful SLE and lupus nephritis trials [12-14].

While the chance of flaring is never abolished, most authors supporting GC minimization underline that the rate of severe flares are comparable across different GC regimens [9], while caveats from higher-degree evidence highlight a significantly higher risk of overall relapse upon GC withdrawal [8]. By comparing patient cohorts in whom observations were carried out, the lack of a durable remission prior to GC withdrawal [15] and the abrupt interruption of even low dose GC emerge as possible determinants of SLE relapses upon GC withdrawal. Additionally, patients who are on low-dose steroids for years, sometimes even decades, are unlikely to be able to stop the drug, not only due to behavioral habits yet to the nearly-irreversible abatement in the pituitary-adrenal axis, which renders these patients dependent on exogenous GC administration. In all patients undergoing long-term GC treatment and especially in those who are unable to taper, attention should be paid to prevention and treatment of GC-related side effects especially on bone and metabolism [16].

The critical reading of available data suggests that a personalized, patient-tailored approach for GC administration and tapering should prevail, figuring out a balance between efficient control of SLE activity and long-term sustainability of treatment.

Key findings

- Low-dose GC regimens are as effective as higher dose regimens in controlling SLE activity while being less burdened with GC-related organ damage [4,7].
- GC pulses activate the non-genomic pathway which has a threshold-mechanism of activation above 100-250 mg intravenous methylprednisolone [2,3], suggesting that such low-dose pulses should be favored
- The use of GC pulses ultimately decreases the cumulative GC dose and might be recommended not only for severe manifestations[7]
- GC withdrawal is a critical process which requires an established disease remission before being attempted [1,10,11]
- Consistent use of antimalarials is helpful in tapering and saving GC in the long term and should be recommended in all patients [1]
- Timely administration of immunosuppressants, either biologics or non-biologics, should be performed for a better control of disease activity coupled with an early steroid-sparing effect [12-14, 17]

Main challenges

While available data on GC management in SLE substantially convene on the need for minimizing GC use whenever possible, several questions remain:

- What is the best candidate patient for GC tapering?
- Is it feasible to pinpoint an ideal timing for GC tapering and withdrawal only based on clinical and laboratory findings, or are histological findings needed?
- Is there a minimum duration and/or degree of remission which allows the safest GC tapering?
- What are the real advantages of GC taper in the long term?
- Are there SLE manifestations/phenotypes which are more likely to relapse upon GC tapering?
- Is there a combination of immunosuppressants with better steroid-sparing capabilities which could be prompted before and in view of GC minimization?
- Can oral steroids be avoided through maintenance therapy for specific manifestations which require long-term treatment, such as LN?

Main unmet needs

Despite a progressive convergence in adopting low-GC imprinted therapeutic regimens and evidence supporting minimization of GC as being advisable in the long term, heterogeneity in GC handling is still common, which is at least partially due to the lack of compelling data pinpointing reliable patient characteristics associated with a safe GC tapering. This pitfall in patient stratification and the fear of future flares generates uncertainty and promotes chronic use of low GC doses, resulting in a relevant cumulative GC burden and further GC-related damage.

Perspectives

The approach to minimal-dose GC regimens for SLE management is being progressively adopted in the scientific community, yet the process needs to be made consistent across different groups and countries. As a first step, the prompt use of immunosuppressants and/or biologics for refractory or severe manifestations should be promoted early enough as part of a steroid-sparing strategy to avoid excessive use of GC [12-14, 17], similarly to a widespread use of hydroxychloroquine, which allows safer GC tapering in the long term [1,4,5,7,15].

Furthermore, the investigation of ideal schemes for safe GC tapering through clinical trials could be coupled with the accurate stratification of patients, based both on clinical and laboratory parameters, also pursuing the chance for endotype stratification. Patients could be classified at the blood and at the tissue level according to their baseline expression of selected GC-responsive genes and/or modifying receptors, which ought to be identified as most meaningul, and by evaluating potential variations of this signature along with treatment administration, using precise medicine tools. Similarly to what is being carried out for targeted medications, the discrimination between better or poorer responders to first line treatment including GC would allow a more tailored tapering strategy in selected patient groups, discarding the habit of chronic GC administration.

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Digital health & lupus

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Context

Last year has been a major catalyst for digital health, accelerating the shift from traditional healthcare models delivered in person to increasingly virtual visits. Yet, digitalization remains one of the most challenging issues faced by patients with autoimmune diseases such as SLE, their physicians and healthcare systems [1]. Digital health technologies, including shared electronic health records (HER), virtual visits, mobile health, wearable technology, digital therapeutics powered by artificial intelligence and machine learning offer enormous potential to improve SLE care, but this potential has so far been largely unrealized.

Key findings

The past decade has seen tremendous development in digital health, artificial intelligence (AI) and machine learning. In the field of rare connective tissue diseases, including SLE. These opportunities enable numerous innovative applications:

- Telemedicine & virtual care, which is a model of care facilitated by a wide range of technologies, including audio and/or video conferencing, secure messaging, and patient monitoring systems, which aims at helping health care providers to deliver care remotely overcoming the constraints of distance, location or time. This leads to the concept of the Hospital at home, which could be crucial for patients with SLE who may live far away from reference centers.
- Computer assisted diagnosis (CAD), in which deep learning methods enable computers to filter data (in particular images [2]) in order to learn how to predict and classify information without human intervention
- Deep phenotyping, prognostic modeling & precision medicine, in which integration of big data sets generated from well-defined SLE cohorts using high-level technological platforms (multi-omics) may help to elucidate underlying disease mechanisms and fuel precision medicine.
- Real-world data & population and public health. Bigdata can provide real-world evidence (RWE) from real-life practice settings for the analysis of SLE progression, drug prescription patterns including adherence to treatment guidelines, drug-induced lupus [4], cost-effectiveness of therapy, safety, as well as into the long-term phenotypes and outcomes of lupus in unselected patients seen in daily practice.
- Patients' perspective, engagement & therapeutic education. Digital health offers immense opportunity to improve our understanding of patients' perspectives and to improve self-management.
- Digital trials. The future of clinical trials has already been impacted by the incorporation of digitally collected PROs. Further, digital endpoints have recently been approved by

regulatory agencies, as key-, secondary- or exploratory endpoints in trials.

- Healthcare system organization. Digital technologies offer significant opportunities to improve the health of SLE patients as well as the healthcare system itself.

Main challenges

Big data is a fast moving field in need of adequate reporting of methods and benchmarking. AI commonly acts as a black box without a proper way to understand how the technology makes its decision, and the results can neither be explained nor easily be replicated. A major barrier to the development of AI technologies in SLE is the very large number of examples required to train the network reliably [3]. A key-point for the acceptability of CAD from the legal and ethical perspectives is that diagnoses suggested by CAD should be always be approved and implemented by a medical doctor and not directly by the algorithm itself. Further, applications of big data and AI raise several legal and health policy considerations, especially in the context of rare diseases, including privacy and confidentiality, informed consent, impact on the organization of the medical profession, and justice. It is therefore crucial to ensure the right governance measures, such as the Health Insurance Portability and Accountability Act (HIPAA) and the European General Data Protection Regulation (GDPR), are in place and evolved to protect individuals. Also, the healthcare industry is a major target for hackers, due to the highly sensitive nature of personal medical information. Cybersecurity of health data is therefore a major challenge. We have recently seen several examples of HER data leak with disastrous consequences. Some of those issues could be solved by the implementation of blockchains, ensuring secure encryption of patient information available only to accredited users. The typical need for high-speed connectivity further emphasizes the highly unequal access to care and digital technologies in the world. Also, in a virtual health setting, questions remain about which healthcare services would return to being in-person and which would continue to expand digitally.

Main unmet needs

- Full digitalization of health records
- Interoperability of data format
- Increased Involvement of SLE specialist in the design of digital tools
- Increased digital literacy for patients
- Enhanced data security
- Robust assessments of the efficacy, affordability and scalability of digital tools in the context of SLE

Perspectives

To achieve the full potential of digital health technologies in SLE, expert physicians will need to be engaged upstream and subsequently incorporate those new tools into routine clinical care for lupus. Numerous companies are addressing various aspects of the digital healthcare ecosystem, resulting in an incredible number of non-integrated non-interoperated digital solutions with which patients are struggling. In particular, interoperability of EHR and wearable data remains a major gap. Despite these limitations, digital health offer enormous potential to improve SLE care, but this potential has so far been largely unrealized.

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