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Editorial

Lupus in the 21st century

Over the years we have witnessed significant innovations in the clinical management of SLE. This supplement will focus on the most recent clinical developments over the last 20 years, building on the legacy of the 20th century. With this aim, a group of renowned SLE experts were asked to approach SLE from a number of perspectives, most importantly the clinical perspective, to provide a comprehensive update for clinicians involved in daily disease care.

As a crucial milestone in the history of lupus, the 21st century saw two large group works aimed at redefining disease classification: namely, the new 2019 EULAR/ACR classification criteria for SLE [1] and the classification criteria of the Systemic Lupus International Collaborating Clinics group published 7 years earlier [2]. In this supplement, Aringer and Johnson [3] clearly retrace the steps of this process.

Both classification systems highlight the importance of the immunological variable in order to classify a patient with SLE. The 2019 criteria took this one step further by placing ANA positivity as an obligatory entry criterion in the classification process. Complement also forms part of the new criteria and has a significant bearing on the final score. Furthermore, especially in the most recent criteria, cutaneous items underwent substantial revisions and the concept of biopsy-proven lupus nephritis (LN) with ANA or anti-dsDNA positivity as a stand-alone manifestation was further refined. Non-infectious fever represents the only entirely new criterion within the EULAR/ACR 2019 classification criteria and helps with early classification.

From a clinical point of view, a significant level of new data has emerged in the last 20 years regarding neuropsychiatric (NP) and renal manifestations. In 1999 the ACR published a standard nomenclature as well as a set of case definitions for 19 NP syndromes in SLE, laying the foundation for renewed scientific interest in NPSLE [4]. Since then there has been considerable scientific focus on the diagnosis and attribution of the wide spectrum of NP events occurring in SLE patients as reviewed by Govoni and Hanly [5].

The new millennium also saw the achievement of certain landmarks regarding the management of LN. First was the publication of a new histological classification system, whose subsequent 2018 revision proved of significant use in standardizing definitions and reducing interobserver variability [6]. Regimens for optimizing efficacy and minimizing drug toxicity have been developed in recent years and Gasparotto *et al.* [7] comprehensively retraced the stages of these recent achievements in LN treatment.

The diagnosis of an autoimmune disorder such as SLE must not ignore the importance of biomarkers. As reviewed by Capecchi *et al*. [8], new data from recent decades corroborate the relevance of traditional biomarkers as well as seeing the emergence of new ones.

One of the key findings of the latter was the increased expression of IFN-regulated genes in blood and tissues from SLE patients, the so-called IFN signature. Data regarding the linkage between the IFN signature and clinical phenotype, disease activity, comorbidities, treatment effects and prognosis have amassed since the year 2000.

In addition, after the initial descriptions at the turn of the 21st century, a new member of the TNF family, designated as B cell activating factor (BAFF), was found to have a central role in the development, maturation and survival of B lymphocytes. Furthermore, BAFF serum levels were also found to be elevated in patients suffering from autoimmune conditions, especially SLE, and may correlate with disease activity.

Evidence of links between biomarkers and disease activity, as well as their involvement in the pathogenetic process, led to them being studied as SLE therapeutic targets. The first successful result of this strategy was the approval of belimumab, a monoclonal antibody targeting soluble BAFF, in 2011 as add-on therapy for active SLE. Since then, evidence has amassed regarding the use of belimumab in clinical practice. The recently updated EULAR recommendations for SLE management names the drug as one of those recommended for extrarenal manifestations resistant to glucocorticoids and antimalarials (with or without conventional immunosuppressives). Moreover, in spite of the failure of phase III trials, a large amount of data from real-life studies supported the use of rituximab both in renal and extrarenal manifestations in refractory or life-threatening cases, thus this is the placing of rituximab as defined by the EULAR recommendations [9].

Ruiz-Irastorza and Bertsias [10] have clearly summarized other developments in the therapeutic arsenal of SLE alongside guidelines for a more rational use of older drugs. In particular, evidence has grown in recent decades on the multiple benefits of antimalarials in SLE as well as highlighting the need to carefully balance the efficacy and toxicity of glucocorticoids. As a result of more recent evidence, a therapeutic algorithm for clinical disease manifestations has been proposed that is not only focused on control of disease activity and prevention of flares, but also prevention of organ damage accrual and complications. This proposal represents a very useful practical guide for clinicians.

The effective use of new drugs cannot be considered without reference to a clear definition of clinically relevant treatment targets. In recent decades, the significant increase of life expectancy observable in SLE patients has enabled the focus to shift to other emerging issues, such as damage accrual, comorbidities and patient quality of life. However, the question of the definition and attainment of such targets is still a matter of debate. In recent years, the activity of the scientific community has led to precise operational definitions for the concepts of disease remission and low disease activity. Golder *et al*. [11] clearly explained that the process of developing treatment targets for a complex and multifaceted disease such as SLE is extremely challenging and is by no means over. Nonetheless, work carried out in recent years has led to the definition of feasible and validated targets constituting the essential basis for implementing a treat-to-target approach in SLE [11, 12].

Despite this, there is still a significant disconnect between observational studies and clinical trials, as the optimal outcome measures to be employed in clinical trials of SLE have yet to be determined. Among the several instruments proposed, the SLE responder index-4 is the preferred primary outcome measure in SLE clinical trials; however, its use in clinical practice is very limited. Thus, a revaluation of outcome measures in clinical trials is necessary to develop a single and more clinically meaningful way to assess the impact of new therapies. In this perspective, the recent scientific initiatives toward the definition of remission and low disease activity state are promising to overcome some of the outstanding issues in SLE clinical trials.

The therapeutic targets of remission and low disease state are based on the degree of disease activity and consequent treatment; however, in no way do they adequately address areas such as health-related quality of life, something that is significantly compromised in SLE patients. Indeed, recent literature has identified that health-related quality of life and, in particular, fatigue are not adequately managed, even in remission, which leads to patient frustration and isolation. Kernder *et al.* [13] highlighted the need for more patient-oriented clinical research to help identify new strategies for patient management, integrating both patient and physician perspectives. Some excellent examples of research in this direction are now emerging and mentioned in this supplement.

Long-term disease outcomes are the natural endpoint of this consideration of lupus in the 21st century as the most reliable reflection of recent developments in SLE treatment. Even though Arnaud *et al.* [14] describe a dramatic improvement in SLE survival in recent decades, increased morbidity and mortality still exists, especially in young patients. Therefore there are several outstanding needs that must be addressed, including numerous areas that depend not only on the disease itself, but on therapies, comorbidities and access to care. For instance, because of the widespread use of HCQ to fight coronavirus disease 2019 (COVID-19), HCQ access issues for patients with SLE occurred in multiple countries during the COVID-19 pandemic, exposing patients to a significant risk of flares [15].

In conclusion, the 21st century has witnessed the introduction of several innovations in the management of lupus patients and has consolidated clinical practice with new evidence. Clinicians can now count on new diagnostic aids, molecules and therapeutic strategies. But more than anything, the 21st century has led us to value strategies that place at their heart the patient, with all their individualities and complexities.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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