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Preclinical and early systemic lupus erythematosus

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A B S T R A C T

The challenge of early diagnosis and treatment is a timely issue in the management of systemic lupus erythematosus (SLE), as autoimmunity starts earlier than its clinical manifestations. Hence, growing efforts for stratification of patients according to the individual risk of developing specific clinical manifestations and/or predicting a better response to a given treatment have led to the proposal of several biomarkers, which require validation for use in clinical practice. In this viewpoint, we aim at distinguishing and discussing the features and the approach to asymptomatic immunological abnormalities potentially heralding the development of SLE, defined as preclinical lupus, and clinical manifestations consistent with SLE not yet fulfilling classification criteria, defined as early lupus. In case of preclinical SLE, careful surveillance using available screening tools is paramount, while patients with early lupus deserve an appropriate and timely diagnosis and, consequently, a proper treatment including hydroxychloroquine as the anchor drug.

Introduction

The starlight seen from the Earth currently was emitted hundreds to several thousand years back in time [1], which means, we currently see the effect of past processes that had begun much earlier than could be detected.

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Similarly, the diagnosis of autoimmune rheumatic diseases remains a challenge as it is frequently dependent on clinical and serological manifestations arising from immunological pathways which took place earlier in time and that are unlikely to be specifically hit by a wide immunosupporession relying on non-targeted therapies. Concerning systemic lupus erythematosus (SLE), growing evidence has shown that the burden of autoimmunity preceding overt disease accumulates progressively with time, thereby moving the border between normality and abnormality from the clinical to the preclinical level and posing the issue on how to correctly diagnose, monitor, and treat patients as well as subjects at risk for SLE development [2].

Classical vs. early lupus

Classical SLE may be better referred to as *classifiable* SLE, meaning a full-blown gathering of signs and symptoms reaching the threshold for SLE classification.

Currently, a new set of American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) endorsed classification criteria is being developed [3], which should better perform in terms of sensitivity and specificity as compared to those of previous sets. Differences between classification and diagnostic criteria have been extensively discussed [4,5], and although the final aim of the classification criteria is not to lead to early diagnosis but rather to frame a homogeneous group of patients, it is worth underlying that this latest version of criteria entails two major differences with previous sets. First, antinuclear antibody (ANA) positivity is introduced as an entry criterion before other items are checked because of the large negative predictive value of this test [6], which is relevant because, paradoxically, some patients classified as SLE could not actually have the disease in case of misuse of criteria sets not demanding for immunological abnormalities. The issue of positive ANA as an entry criterion for SLE classification was extensively discussed, with major points regarding potential discrepancies between laboratory techniques for ANA dosing, which may provide inconsistent results [7,8], as well as the occurrence of an exaggerated rate of positive tests when using a low threshold for dilution, especially when ANAs are widely tested in a neutral population where the pretest probability of having SLE is very low [8]. In fact, the meaning of a test in terms of indicating the likelihood of a person being affected with a given disease is influenced by the prevalence of that disease in the population of origin [9], i.e., the a priori (pretest) probability of having the disease just because he or she comes from a high- or low-risk population. Regarding SLE, the pretest probability of having the disease is increased in the presence of red flags including female gender, childbearing age, arthralgia or arthritis, skin rash, alopecia, Raynaud's phenomenon, fatigue, and serositis and sicca syndrome [10]; therefore, positive ANA in the presence of these flags gains a more defined meaning rather than the same positivity being encountered in low-risk subjects, in whom alternative reasons for positive ANA are more likely than SLE. On the other hand, the concern of ANA-negative patients with SLE was also discussed [8,11]. With regard to this, however, it should be recalled that positive ANA is required by classification criteria to homogeneously gather truly affected patients and not to diagnose the single individual. True-negative ANA tests among patients with SLE are remarkably rare at onset and questionable even throughout the disease course, when, however, ANA titer may be affected by previous intensive treatments as well as by the aforementioned discrepancies in ANA measurement [8]. Moreover, extranuclear localization of nosologically defined nuclear antigens may occur, which may lead to false-positive results [8,11]. With regard to this, a solution was proposed to use different and novel techniques such as the solid-phase assays to confirm a positive or a negative result during the diagnostic process [8,12], provided that the test is performed in individuals suspected to have SLE or related diseases and not as wide screening. However, double testing may not be performed equally in all countries; hence, starting from a positive ANA test would maximize the inclusion of most truly affected subjects, who will then have to be individually investigated.

As the second and most important difference of the new criteria set as compared to previous ones, items have been weighed and SLE is classified on a continuum of values with a threshold for disease classification of 10 points. This method gives relevance to either of the more specific features of the disease that has a greater weight, potentially allowing for an earlier classification of patients who will not necessarily need to accrual several symptoms/abnormalities to overcome the threshold of 10 [3].

Scrolling through the items listed among classification criteria, individual items weighing ≥5 include arthritis, acute pericarditis, acute cutaneous lupus, proliferative or membranous nephritis, anti-Sm and anti-double-stranded (ds)DNA antibodies, seizures, and pleural effusion, suggesting that in the presence of any of these signs or laboratory abnormalities, a diagnosis of SLE should be at least suspected and opportune examinations undertaken to investigate the clinical picture in more detail. Interestingly, fever was introduced as an item for classification, apparently with a lower weight, officially paving the way to SLE as an option to think about in the case of unexplained fever.

Altogether, these aspects are relevant and may possibly lead to an earlier diagnosis of a greater number of patients, resulting in an earlier treatment that heralds a better prognosis (discussed below). Moreover, it is time to overcome the concept of "early" or "incomplete" lupus intended as a benign form of the disease, as these terms were coined to describe subjects with clinical and preclinical features consistent with those of SLE, yet not fulfilling classification criteria, while being not necessarily meant to define a milder disease course [13]. Instead, in many cases, patients with few signs and symptoms are already affected with an initial yet full-blown SLE and, as such, should be diagnosed and treated accordingly.

Preclinical alterations: cytokines and autoantibodies

According to different cohorts and laboratory techniques, the prevalence of ANA in the healthy population is estimated to be approximately 5% at high titer (>1:160) [14], increasing to above 20% when considering lower titers in the female population [15]. It is worth noting that increasing ANA titers entail a greater specificity [6], and interestingly, their diagnostic accuracy is increased from 58% to 84% when coupled with the dosage of serum levels of interleukin (IL)-5, IL-6, and interferon (IFN)-γ [16].

Beyond ANA, previous data suggest that subjects at major risk for full-blown SLE already harbor a greater burden of autoreactivities versus individuals who are less likely to progress, i.e., they display a higher penetrance and higher titers of more specific autoantibodies such as anti-dsDNA, anti-Sm, or other nuclear specificities [15,17]. Additionally, two retrospective studies investigating previously stored serum samples of patients with actual SLE detected the appearance of a growing number and specificities of autoantibodies closer to clinical disease onset, e.g., anti-dsDNA appeared 1.2 years before onset, while anti-SSAs were detectable already approximately 4 years before, suggesting a rather ordered sharpening of the autoimmune setting [18,19]. More recently, a cross-sectional report suggested that an increased IgG:IgM anti-dsDNA ratio, especially in the presence of C1q deficit, may be associated with SLE development [20], which should be tested longitudinally.

Several best-known autoantibodies are used as biomarkers of disease activity and monitoring, i.e., measurable indicators of a biological process (physiologic or pathogenic) and/or of a response to an intervention aimed at modifying that process [21]. With regard to this, anti-dsDNA antibodies are still largely used in aiding SLE diagnosis owing to their specificity reaching 95% and their association with renal involvement [22]. However, they can be found in other conditions such as infections or malignancies and in the elderly population [23], and conflicting data on their consistency in SLE diagnosis [24] and as flare predictors [25] were reported, also owing to diverse laboratory techniques, which challenge general reliability [26]. Notwithstanding these findings, anti-dsDNA antibodies remain among the most handy and useful tools for patient monitoring.

The panel of SLE-specific biomarkers includes other antibodies such as anti-Sm and anti-ribosomal P antibodies, displaying high specificity but low sensitivity [27]; anti-C1q; and the emerging anti-nucleosome antibodies, which are tested in real-life settings because of their correlation with global and renal disease activity [28]. Among proposed diagnostic biomarkers within the autoantibody pool, those reaching a decent degree of reproducibility mostly concern renal involvement [29]. Combination of anti-C1q and anti-dsDNA antibodies with decrease in complement has been strongly associated (OR 14.59) with lupus nephritis (LN) [30] with a corresponding low likelihood of renal disease in the absence of both [31]. Among novel specificities, anti-pentraxin3 (PTX3) antibodies are emerging as protective against LN development [32,33].

A growing bulk of evidence has shown that even earlier changes in proinflammatory cytokine levels [16,34] long precede the onset of clinical manifestations. In fact, IFN-γ levels increase >3.5 years before

SLE diagnosis, and IFN-γ itself was shown to promote the generation of interferogenic anti-RNA antibodies, which, in turn, could induce the surge in IFNα and subsequent effects [34]. Consistently, increases in IFN-γ levels were shown to characterize transition from undifferentiated to definite connective tissue disease [35]. Furthermore, a comparison of ANA-positive subjects with age-matched ANA-negative subjects and patients with full-blown SLE revealed a stepwise increase in the expression of pro-inflammatory cytokines, namely, IFN-γ, IL-17, and TNF, while patients with SLE only were shown to display high levels of IFN type I [36], in keeping with known and emerging roles of IFN type I in disease development and self-maintenance [37].

Details of emerging lupus biomarkers are summarized in Table 1 [22,23,26,28,30,31,38–50].

Early clinical symptoms

Signs and symptoms in patients at early stages of SLE have been frequently analyzed [51–54], retrieving a high prevalence of nonspecific manifestations at onset, such as fever, arthralgia, or skin rashes in most cohorts, with a progressive accumulation of both clinical and serological features even in the first stages of the disease [51]. In fact, it was suggested that progression to defined SLE (i.e., ≥4 current classification criteria) during a follow-up ranging from 2.2 [55] to 6.3 years [56] involves up to 20% of individuals displaying suggestive immunological and clinical features including malar rash, photosensitivity, proteinuria or urinary casts, oral ulcerations, anti-dsDNA antibodies, reduced C3, increased immunoglobulin G (IgG) autoreactivity, and antiphospholipid (aPL) positivity [27,55,56]. Conversely, the proportion of asymptomatic autoantibody-positive subjects actually progressing to SLE remains barely predictable.

With regard to this, one study longitudinally followed up 409 relatives of lupus patients, the majority of whom were asymptomatic and displayed 0 or 1 ACR criteria at baseline [57]. After a mean follow-up of 6.4 years, 11% transitioned to full-blown SLE. Compared to the 89% who did not develop SLE, this 11% showed a baseline imbalance between pro-inflammatory versus anti-inflammatory cytokines and a greater variety of SLE-associated autoantibodies, while there was no difference in the proportion of ANA-positive subjects [57], thus challenging ANA reliability in a wide horizontal screening [9]. Rather, screening for ANA and subsequent specificities should be prompted in subjects (especially in women of childbearing age) already bearing some red flags for systemic autoimmunity, which have been described in the scientific literature and may be pinpointed as arthralgia or arthritis, skin rash, alopecia, Raynaud's phenomenon, fatigue, serositis and sicca syndrome [10], extending to pericarditis or nephritis [3]. Frequency of the follow-up should be also improved that subtle changes are captured [27].

Differential diagnosis in early stages of disease

It should be mentioned that specific autoantibodies may be very helpful to the diagnosis even at disease onset, so that the initial diagnosis of SLE may be performed with a reasonable degree of certainty in the presence of symptoms accompanied by typical immunological abnormalities, e.g., anti-dsDNA or anti-Sm antibodies. Nevertheless, some pictures may be blurrier and require exclusion of potential lupus mimickers, i.e., conditions that may resemble SLE in terms of clinical features and/or laboratory abnormalities to finally diagnose SLE (Fig. 1, [58–60]). The most common mimickers are reported to be viral infections, especially Parvovirus B19, whose clinical picture with rash, arthralgias, fever, and increased ANA titer may easily suggest SLE [58,60].

In such cases, it is worth considering the speed of onset, which is usually fast in viral infections, as well as its occurrence mostly in children, increase in acute phase reactants, and the absence of major manifestations such as glomerulonephritis.

Among autoimmune rheumatic conditions, skin rash in dermatomyositis may be misleading, although localization may distinguish it from lupus, depicting heliotrope rash, Gottron's signs, or papules and a generalized swelling of the erythematous surfaces.

Importantly, differential diagnosis is a continuously developing process in SLE, as it is often more challenging to later distinguish a disease relapse in established lupus from an intervening infection or complication [51,61,62], which requires different therapeutic approaches.

Table 1
Measurable serum and urinary biomarkers in SLE.

Biomarker		Proposed function	Ref.
Used in clinical practice			
Renal	Anti-dsDNA antibodies	Serum levels directly correlate with disease activity, especially renal involvement	[22,23]
	Anti-nucleosome	Association with renal involvement	[28]
	Anti-C1q	Association with renal involvement	[30,31]
Nonrenal	C3, C4	Serum levels inversely correlated with active disease	[23]
	Anti-ENA antibodies	Association with peculiar manifestations, e.g., photosensitivity, arthritis, and neuropsychiatric involvement	[26]
	Anti-histone	Association with disease activity Association with drug-induced lupus	[38]
	MCP-1	Serum and urinary concentration correlate with SLEDAI	[39]
Emerging			
Renal	Anti-PTX3 antibodies	Inversely associated with renal involvement	[31]
	Urinary CD4 T cells	Active nephritis	[40]
	Haptoglobin Alpha 1 Anti-chymotrypsin RBP	Active nephritis	[41]
	Urinary miR 3201, 1273a	Down regulation in active LN and associated with endocapillary inflammation	[42]
	miR-193a-5p, −423, 501-3p, and −874	Upregulated in active proliferative lupus nephritis	[43]
	NGAL	Serum and urine concentrations are higher in active renal involvement	[44]
	MCP-1	Urinary concentration correlated with proteinuria	[39]
	CXCL16 suPAR	Association with active renal lesions	[45]
Nonrenal	CXCL16	Association with disease activity	[45]
	suPAR	Association with disease activity and pulmonary involvement	[45,46]
	Anticarbamylated proteins	Association with articular involvement	[47]
	IP-10	Association with pulmonary involvement serum levels changing with nonrenal flares	[46,48]
	SIGLEC-1	Correlation with disease activity and nonrenal flares	[48]
	sCD40L	Association with arterial thrombosis	[49]
	Osteopontin	Correlation with disease activity in new-onset SLE	[50]

SLE systemic lupus erythematosus; dsDNA double-stranded DNA; C1q complement fragment 1; C3, C4 complement fragments; ENA extractable nuclear antigens; MCP-1 Monocyte chemoattractant protein-1, PTX3 pentraxin 3; miR micro-RNA; NGAL neutrophil gelatinase-associated lipocalin; CXCL16 Chemokine (C-X-C motif) ligand 16; RBP retinol-binding protein; suPAR soluble urokinase-type plasminogen activator receptor; IP-10 IFN-γ-inducible protein-10; SIGLEC-1 sialic acid-binding Ig-like lectin 1; sCD40L soluble CD40 ligand, SLEDAI SLE disease activity index.

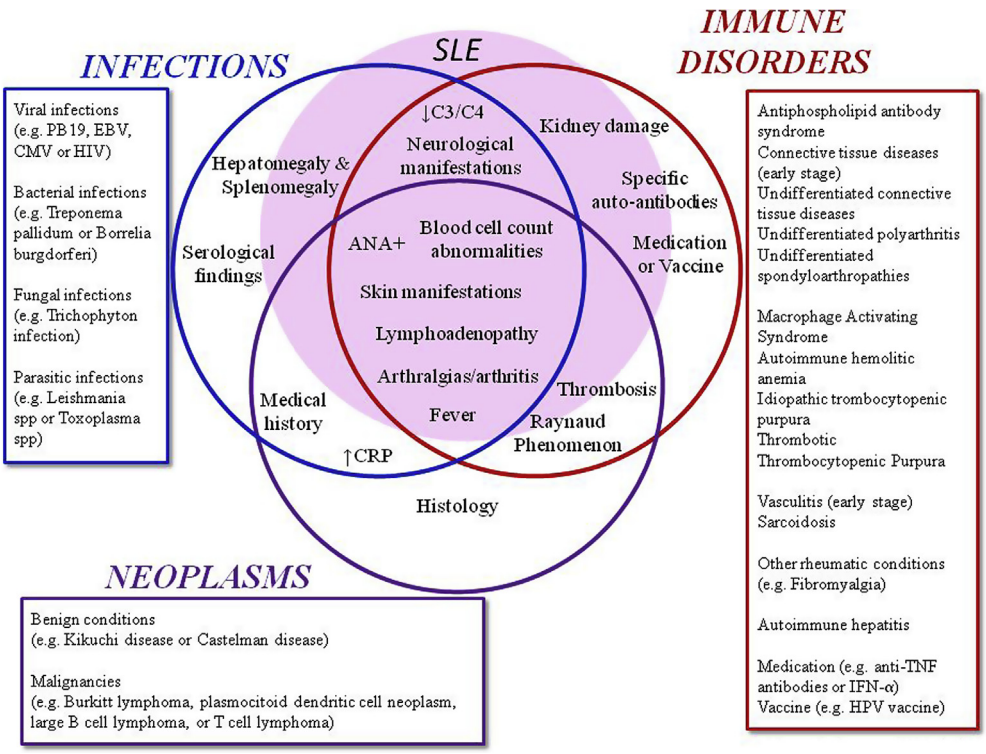

Fig. 1. Common lupus mimickers to be ruled out at diagnosis mostly include other autoimmune disorders, infections, and neoplasms, which share some laboratory and clinical abnormalities with SLE (pink circle). SLE systemic lupus erythematosus; CRP C-reactive protein; ANA antinuclear antibodies; TNF tumor necrosis factor; IFN interferon; HPV human papilloma virus; EBV Epstein–Barr virus; CMV Cytomegalovirus; HIV Human immunodeficiency virus; PB19 Parvovirus B19.

Early treatment

The main goal of an early adequate treatment is to avoid long-term complications arising from delayed therapy, that is, irreversible organ damage or eventually death, whose rate was increased in patients with LN undergoing delayed biopsy and related treatment [63].

Additionally, a retrospective longitudinal matched-cohort study of more than 9000 patients with SLE showed that patients diagnosed within 6 months from onset of clinical symptoms exhibited a lower number of flares as well as a lower rate of hospitalization and overall SLE-related costs than matched patients diagnosed >6 months from clinical onset [64]; this suggests that the earlier the intervention, the greater is the protection from disease-related damage.

Approach to subjects with preclinical lupus

Subjects with pure preclinical abnormalities, by definition, do not show any clinical symptoms related to SLE; however, incidental retrieval of ANA or other positive autoantibody tests in asymptomatic population may occur due to a number of reasons, despite the fact that widespread ANA screening is not recommended [9]. In case this occurs, an accurate examination and collection of data and medical history are paramount [65] to proceed with a first determination of a potential risk profile for actual disease development. Concomitantly, common or related conditions that may associate with positive ANA, such as autoimmune thyroiditis or even viral infections, should be excluded [9].

When this is done, the fact remains that no shared strategies for primary prevention are released, as there is no evidence that a pharmacological treatment in asymptomatic ANA-positive subjects may prevent the onset of an overt disease, although retrospective evidence has shown that treatment with antimalarial agents could delay the onset of clinical manifestations in individuals at risk [66]. However, any drug, including antimalarial agents, entails the potential risk of adverse events [67]; hence, a risk–benefit approach should be adopted based on single patient stratification. Thus, in asymptomatic subjects bearing a persistently low positive ANA with no other abnormalities, tight monitoring may be enough, together with removal of potentially triggering factors such as exaggerated sunlight exposure, smoking, or SLE-inducing drugs.

Conversely, in asymptomatic subjects bearing already an enriched autoimmune background with persistent high titers of ANA and/or SLE-associated or specific autoantibodies, e.g., anti-dsDNA or anti-ENA and/or complement consumption, proposing antimalarial agents may be rational, as these people are at higher risk for disease progression [27]. Additionally, the use of vitamin D as an immunomodulator in subjects at risk for systemic autoimmunity is endorsed by some experts [68] despite no large randomized controlled studies available.

Primary prevention in asymptomatic carriers of aPL antibodies is another challenging point, as chronic administration of antithrombotic treatment may entail a significant risk of bleeding. Nevertheless, despite the failure of the only randomized controlled trial (RCT) investigating the administration of low-dose aspirin in asymptomatic aPL subjects [69], a panel of experts have agreed on the usefulness of low-dose aspirin in primary thrombosis prevention in asymptomatic aPL carriers [70,71], especially when multiple antibody specificities and/or isotypes accumulate (IgG or IgM anticardiolipin, IgG or IgM antiB2GPI, and lupus anticoagulant) and/or high titers are present, as, in these cases, the likelihood of thrombosis is increased [72]. Additionally, in the case of a potentially precipitating condition, e.g., pregnancy, surgery, or prolonged immobilization, a time-limited antithrombotic prophylaxis should be in our view considered in all asymptomatic aPL carriers. Despite no dedicated data or opinion available for patients with SLE with an associated positive aPL positivity, the adoption of the same expert recommendation seems suitable.

Similar to the removal of triggering factors for autoimmunity in asymptomatic autoantibody carriers, removal of modifiable prothrombotic risk factors should be performed in asymptomatic aPL carriers, as well as screening for genetic risk alleles that may exponentially increase the risk for thrombosis.

Approach to early clinical SLE

Subjects bearing frequent and nonspecific symptoms, e.g., arthralgia/arthritis or Raynaud phenomenon, without a strong laboratory signature, e.g., no specific or highly suggestive lupus antibodies, are often referred to as undifferentiated connective tissue disease (UCTD), whose nomenclature was recently critically reviewed [73], as the potential evolution to a definite CTD is sometimes overlooked and these patients may also develop organ damage [74,75]. As the highest rate of evolution into a definite CTD is reported within the first 3–5 years from the onset of UCTD [76,77], a tighter follow-up in this timeframe could be useful to promptly detect any accumulating abnormalities and optimize treatment. Interestingly, no practice guidelines are currently dedicated to UCTD management, even though these subjects are actually patients with clinical complaints, and as such, it may be rational to treat them with antimalarial agents as background treatment [78], alongside close surveillance.

Moving a step forward, patients displaying signs or symptoms related to SLE with a consistent serology may be correctly diagnosed as affected with SLE even in the absence of a full set of classification criteria and should be treated accordingly.

There are a number of arguments regarding the beneficial effects of antimalarial agents in hampering the progression of active SLE and accumulation of long-term damage [67,79–81], although there are conflicting data regarding a strong effect in terms of flare prevention in the long term [82,83] and a clear threshold for therapeutic efficacy was not univocally pinpointed [82,84]. However, given the wide range of therapeutic effects of antimalarial agents including a possible antithrombotic and antiproliferative function [67] and the overall exceptional tolerability, these drugs are highly recommendable in all lupus patients in the absence of absolute contraindications. Moreover, antimalarial

agents are thought to hinder aberrant immune responses by interfering with acidic lysosome formation and autoantigen processing and presentation, and their use was associated with impaired IFN-alpha production by plasmacytoid dendritic cells in patients with SLE [85], overall exerting a long-standing immunomodulating effect without triggering a relevant immunosuppression, which renders them suitable for long-term use starting since early phases of the disease. Risk of retinal toxicity, which is the most commonly advised during chronic use of antimalarial agents, was recently assessed as being really low in subjects with normal renal function who were administered a threshold dose of 5 mg/kg/day of hydroxychloroquine during the first years of treatment, requiring an ophthalmologic assessment at baseline and, then after five years, according to the American Ophthalmology Society recommendations [86]. This interval may be decreased to one year for the subsequent years of therapy, as risk for retinal toxicity increases with cumulative dosage and treatment duration from the fifth year onward, remaining, however, still low, i.e., approximately 1% at 10 years [86].

Prevention of comorbidities related to disease activity and/or treatment should be considered from the commencement of the first therapeutic steps, thus avoiding excessive steroid misuse and providing performance of adequate screening for infections, bone protection, and malignancy surveillance [2,87,88].

Finally, it must be underlined that the lag time between SLE onset and diagnosis has become progressively shorter owing to the discovery and correct performance of autoantibody testing [27], so that severe manifestations for which immunosuppression is needed are less likely to be present at disease onset [89]. However, the use of immunosuppressants early during the disease course may still be required for moderate yet refractory and steroid-dependent manifestations, e.g., persistent cytopenias or relapsing arthritis, for which appropriate use of immunosuppressive steroid-sparing drugs should be performed.

A proposed algorithm for the management of early SLE is depicted in Fig. 2.

Patient stratification

Stratification of lupus patients is a huge challenge grounded on the principle that particular features may predict specific manifestations and increased responsiveness to specific therapies. A first step in

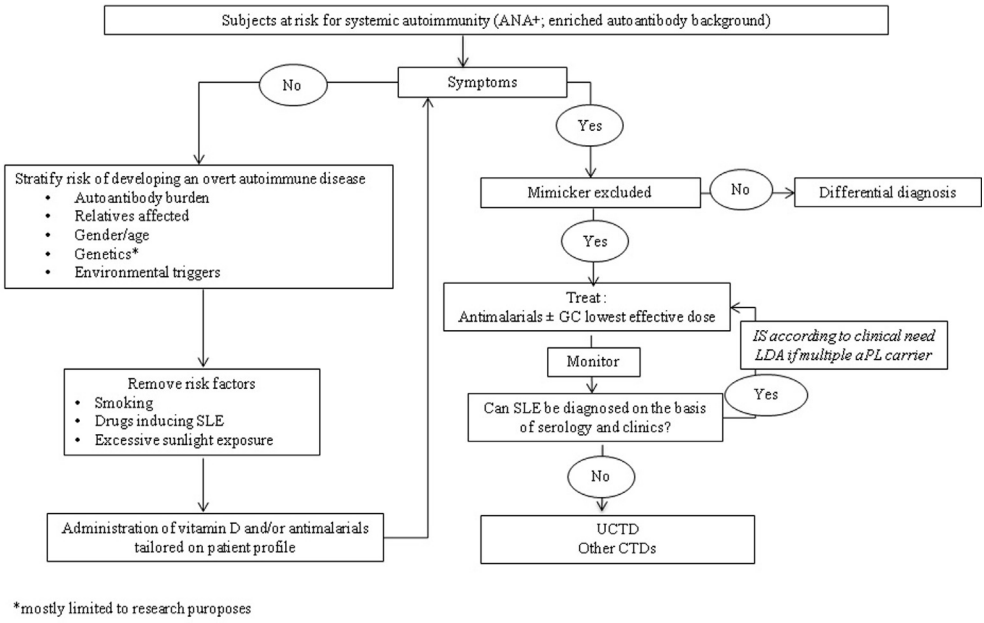

Fig. 2. Proposed approach to early/preclinical SLE. ANA antinuclear antibodies; GC glucocorticoids; SLE systemic lupus erythematosus; UCTD undifferentiated connective tissue diseases; aPL antiphospholipid antibodies; LDA low-dose aspirin; IS immunosuppressants.

patient stratification can be made on the basis of actual clinical features, assuming those may be sustained by homogeneous immunological alterations, as suggested by the successful phase II RCT on ustekinumab and baricitinib [90,91], in which patients were stratified according to the presence of arthritis or cutaneous involvement – although those RCTs deal with overt SLE and are therefore outside the topic of this commentary.

In contrast, a different approach is currently aiming at earlier identification of preclinical abnormalities, which may associate with further disease development and/or response to specific therapies. This process requires more than measurement of biomarkers. Indeed, to stick to the initial metaphor of seeing light released from a star long ago, stratification of patients is like coming closer to the star because we can detect the effect of the initial immunopathogenic change sooner after it has taken place.

Personalized or precision medicine is aided by the development of techniques investigating genetic, epigenetic, post-translational, and metabolic changes (the so-called "-omics"), which may influence patient clinical course and potential response to a given treatment, resulting in baseline stratification of patients who are not yet clinically meaningfully different [92].

Currently, most evidence has highlighted a likely clustering of patients with SLE according to genetic variants of several loci, with the bulk of information referring to type I IFN as well as to neutrophil signature, which would correlate with disease activity and/or specific clinical manifestations such as LN [93–95]. A recent study by the group of Alarcon-Riquelme could in fact retrieve three main genetic clusters in two separate cohorts of pediatric and adult patients with SLE yielding 777 and 1051 significant genes, respectively, who displayed a similar behavior according to specific cell signatures [96]. Particularly, adult or pediatric patients showing a neutrophil signature had the greatest incidence of LN, suggesting a direct risk between the neutrophil-driven clusters and development of renal inflammation, while a third cluster with prevalence of lymphocyte-related genes displayed other clinical features including photosensitive rash and hepatic abnormalities. It is worth noting that percentages of lymphocytes and neutrophils as well as IFN-related genes showed an opposite trend among different clusters even in patients scored with similar disease activity with the SLE disease activity index (SLEDAI) score, thus highlighting a discrepancy between available tools for clinical monitoring and abnormalities affecting genetic pathways, which may herald specific manifestations. Similar results had been previously retrieved in a pediatric cohort of 158 patients in whom the transcriptome was longitudinally analyzed pinpointing 5 immune signatures, whose combination further identified 7 subgroups of patients [94]. Among those, IFN signature strongly correlated with disease activity and development of LN.

Active LN was also addressed by a larger study on urinary peptidomics [97] finding a 65-urinary peptide SLE-specific panel that showed a sensitivity of 83% and a specificity of 73% in discriminating LN versus non-LN patients, overcoming the performance of anti-DNA, C3, and C4, when tested alone [29,97]. Moreover, recent evidence showed that urinary NGAL (neutrophil gelatinase-associated lipocalin) and MCP-1 (monocyte chemoattractant protein-1) are markedly increased among patients with LN and that MCP-1 would also increase before renal flares, positively correlating with disease activity or proteinuria and inversely correlating with glomerular filtration rate and complement levels [42,44]. Some other candidate biomarkers that may associate with specific manifestations were characterized through proteomic studies, and importantly, they were validated in different patient cohorts, e.g., cytokeratin 18, cytokeratin 19, albumin, and annexin A5 in renal samples of LN or anti-aGDI antibodies in neuropsychiatric SLE [98]. Biomarkers for prospective follow-up are in any case scarce despite some evidence reporting that IFN-γ-inducible protein-10 (IP-10) and sialic acid-binding Ig-like lectin 1 (SIGLEC1) correlate with disease activity, playing therefore a possible role in longitudinal disease monitoring [46].

As expected, the association of multiple biomarkers reinforces the likelihood of SLE diagnosis, and development of a composed algorithm to predict disease flares by taking into account differently weighed baseline biomarkers was successfully attempted in a recent study [99], highlighting a baseline increase in innate (IL-1α, IFN-associated chemokines, ICAM, and sCD40L) or adaptive immune mediators belonging to the Th1 and Th17 profile as reliable predictors of flare within 6–12 weeks. These clues are relevant, and although they need validation in different cohorts, a next clinical applicability of measurable risk features may be hoped.

Summary

In conclusion, the mainstays that can be applied to early SLE management at present may be summarized in the following major points: i) tight follow-up of subjects displaying a susceptible serology with persistent high-titer ANA and/or multiple positive autoantibody tests and/or complement consumption, with possible timeframe being defined as yearly check of serology unless clinical symptoms occur, in which case the interval needs to be narrowed to few months; ii) removal of triggering/precipitating factors contributing to the onset of systemic autoimmunity; iii) early treatment with hydroxychloroquine from the time of early clinical manifestations, to be continued if not absolutely contraindicated; iv) asymptomatic individuals who bear multiple positive autoantibody tests may be treated with vitamin D and/or hydroxychloroquine; and v) in silent aPL carriers, low-dose aspirin should be considered according to physician opinion related to the risk profile of the given patient.

Conflicts of interest

The authors declare no conflict of interest.

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Practice points

- Asymptomatic individuals displaying serological and clinical abnormalities consistent with SLE should be carefully monitored and correctly diagnosed as early as possible
- Treatment with antimalarial agents should be initiated from the early stage of disease
- Approach to preclinical lupus should include removal of triggering factors and risk stratification for further disease development
- Pharmacological intervention in asymptomatic subjects is not supported by evidence and must be based on discussion between physician and patient; however, primary prophylaxis of asymptomatic high-risk aPL carriers is recommended by expert opinion
- Prevention and treatment of disease- and therapy-related comorbidities should be initiated early during the disease course

Research agenda

- Validation of emerging biomarkers for disease monitoring and predictive capability is strongly required for systematic use of some biomarkers in real life among the many proposed thus far.
- The pursuit of a personalized medical approach should be further tested in clinical trials stratifying patients according to shared immunological and/or clinical features.
- The widespread use of homogeneous techniques for laboratory testing and consistent ranges for laboratory values across different countries would be helpful in standardization of acceptable thresholds for biomarker assessment and eventually decision making.

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