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From incomplete to complete systemic lupus erythematosus; A review of the predictive serological immune markers

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex and heterogeneous autoimmune disease. A main challenge faced by clinicians is early identification of SLE, frequently resulting in diagnostic delay. Timely treatment, however, is important to limit disease progression, and prevent organ damage and mortality. Often, patients present with clinical symptoms and immunologic abnormalities suggestive of SLE, while not meeting classification criteria yet. This is referred to as incomplete SLE (iSLE). However, not all these patients will develop SLE. Therefore, there is need for predictive biomarkers that can distinguish patients at high risk of developing SLE, in order to allow early treatment. This article reviews the current literature on immunological changes in patients with stages preceding SLE, focusing on autoantibodies, type-I and -II interferons, and the complement system. We also provide an overview of possible predictive markers for progression to SLE that are applicable in daily clinical practice.

Introduction

Systemic lupus erythematosus (SLE) is a complex and heterogeneous autoimmune disease characterized by inflammatory organ involvement and antinuclear antibody (ANA) formation. The exact pathogenic mechanism of SLE has not been fully elucidated, however, genetic predisposition combined with environmental factors like hormonal changes and viral infections disturb the refined balance of the immune system and autoimmunity [1].

A main challenge faced by clinicians is early identification of SLE. Recognition of SLE is hindered by both the heterogeneous character of the disease and overlap of symptoms with other diseases, frequently resulting in a diagnostic delay [2]. Timely treatment however is important, in order to limit further disease activity, and prevent organ damage and mortality [3,4].

The heterogeneous character of the disease is one of the factors hindering formulation of a precise definition of SLE [5]. Also, there is no molecular test that is pathognomonic to SLE. It is important to acknowledge the difference between classification and diagnosis of SLE [6]. Diagnosis is based on clinical findings and immunologic features, and is assigned by a clinical expert. Classification on the other hand is a standardized definition, based on consensus and is mainly constructed for research aims, in order to create consistent and comparable results among research groups.

For many years the American College of Rheumatology (ACR) criteria have been used for classification of SLE [7]. In 2011, Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria were introduced in order to improve sensitivity and specificity [8]. In both criteria sets, disease classification is based on cumulative immunologic and clinical features. Recently, new classification criteria have been published by a European League Against Rheumatism (EULAR)/ACR collaboration [9]. Presence of ANA at a titer of $\geq$1:80 is used as entry criterion. Furthermore, scoring of clinical and immunological features is organized in 10 domains. The classification of SLE is fulfilled when the total score is at least 10 points. In a validation cohort, these criteria reached sensitivity of 96% and specifity of 93% [9].

The clinical manifestations of SLE can occur suddenly, but often symptoms develop over a longer term. Patients can display clinical symptoms and immunologic abnormalities pointing to SLE, while they do not meet classification criteria. Not all, but 10–55% of these patients will progress to classified disease [10–14]. Here, the designation “incomplete systemic lupus erythematosus” (iSLE) will be used for this condition, but many other terms can be found in literature: “early lupus”, “possible lupus”, “latent lupus”, “probable lupus”, and “incomplete lupus” [15]. Research studies that focus on iSLE patients are of special interest, since such data could provide more insight in the immunological changes that precede SLE. Secondly, these patients use less immunosuppressive drugs, which allows investigating the disease process while avoiding drug effects. Longitudinal investigation of iSLE could also reveal immune markers that distinguish patients with persisting low disease activity from those

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who will develop serious organ involvement. At last, next to gaining more insight in the development of SLE, potentially, the pre-stage of SLE also provides an opportunity to slow down or even halt the autoimmune process.

Therefore, the current review provides an overview of the literature on immunological changes in patients with stages preceding SLE. Studies are included that address subjects at high risk for SLE, or with incomplete SLE. Also, serological data of patients who develop SLE during inclusion in population or cohort studies are added. The aim of this literature selection is to identify potential serological markers that are easily applicable in daily clinical practice and could predict a future diagnosis of SLE in order to prevent further disease progression.

Search strategy

We searched PubMed for manuscript titles containing the following terms: lupus AND (probable OR onset OR latent OR incomplete OR early OR preclinical). We filtered the outcome by "English language" and "Human".

This search strategy yielded 880 manuscripts on 8 April 2020. The titels were screened in order to identify relevant articles for the current review question. Furthermore, relevant manuscripts cited within these articles were selected.

Serological markers in iSLE, described per subcategory

Autoantibodies

Retrospective data from two SLE-cohort studies have shown that autoantibodies can be present long before symptoms occur [16,17]. In both studies, blood samples were available up to 9.4 years prior to the diagnosis. In one study, serum of 130 individuals who later developed SLE was collected as part of routine health assessment in a US military cohort. In the other study, sera of 35 pre-SLE patients were derived from a European medical biobank and a maternity cohort. Among individuals who developed SLE, the majority had detectable ANA preceding the diagnosis: 88% in the US study and 63% in the European study. In both studies, anti-SSA antibodies were the first detectable autoantibodies at a mean of 3.7 years before SLE classification in the first, and even 8.1 years in the other study. More specific for lupus, anti-dsDNA antibodies were detectable at an average of 2.2 years, and 6.6 years, respectively, before SLE classification. Remarkably, positive anti-Smith (anti-Sm) antibodies and anti-RNP antibodies, which were only present in a minority of patients, were detectable closer to the diagnosis (1.5 and 0.9 years, respectively). Overall, autoantibody diversity increased towards the diagnosis, as shown by the mean number of autoantibodies per patient that rose from 1.5 to 2.6 in the time before the classification of SLE in the US military cohort and from 1.4 to 3.1 in the European cohort.

Not only for pre-SLE, but also for iSLE patients, the predictive potential of autoantibodies for disease progression has been assessed. In one study including 87 patients with iSLE, 8 (9%) developed SLE after a mean of 2.2 years, and in another study on 264 iSLE patients, 21% progressed to SLE after a mean of 6.3 years [10,14]. Anti-dsDNA antibodies in both study groups were expressed significantly more often in patients who progressed to SLE when compared to the non-progressors. In the first mentioned study, 3 of 8 (38%) SLE progressors had increased anti-dsDNA at baseline, against 4% of the subjects with continuing incomplete SLE. In the second mentioned study, 43% of the subjects who progressed to SLE had increased anti-dsDNA levels, against 14% of the remaining subjects. In another, prospective study of only 28 iSLE patients, but with long mean follow up of 13 years, 6 of the 16 patients who progressed to SLE (38%) had detectable anti-cardiolipin antibodies at baseline. Notably, none of the patients who still had unclassifiable disease at follow up had detectable anti-cardiolipin [11]. In another, prospective study, unaffected first- and second-degree relatives of SLE patients (n = 409) were included as "at risk individuals" [24]. After a mean time of follow up of 6.4 years, 45 (11%) developed SLE. The percentage of ANA-positivity at baseline was significantly lower in unaffected relatives who did not develop SLE (48%), versus the transitioned relatives (89%). Those subjects who progressed to SLE furthermore had higher ANA-titers and anti-SSA titers and more autoantibody specificities, and also were more likely to have anti-RNP antibodies at baseline.

Autoreactive antibodies can be of different isotypes. IgG autoantibodies are considered to be pathogenic, while autoreactive IgM has been suggested to be protective of autoimmune disease development [18,19]. Interestingly, iSLE patients were found to express higher levels of autoreactive IgM than SLE patients [20,21]. Also, IgG:IgM ratios of anti-nuclear autoantibodies showed a stepwise increase from healthy individuals, patients with cutaneous lupus, and SLE patients [22]. The same finding applies to a study in which IgG:IgM anti-dsDNA antibody ratio was lowest in healthy controls, higher in unaffected relatives of SLE patients and again highest in SLE [23]. These findings suggest that seroconversion from autoreactive IgM to autoreactive IgG is associated with progression to manifest SLE and that this might be a predictive factor.

In conclusion, autoantibodies can be present many years before the clinical manifestation of SLE. Anti-SSA antibodies and ANA seem to appear first, but are not specific to SLE development. Towards diagnosis, increasing antibody diversity, such as the appearance of anti-Sm, anti-RNP and anti-dsDNA can be seen. Presence of anti-dsDNA and anti-cardiolipin antibodies, increasing antibody diversity, as well as increasing IgG:IgM autoantibody ratio, are all associated with progression to SLE. However, the studies cited have limited sample sizes. Therefore, the precise positive and negative predictive values of these autoantibodies in iSLE can not be calculated from these studies.

Interferon-type I and II expression and related soluble mediators

The majority of SLE patients display increased expression of IFN-inducible genes in peripheral blood mononuclear cells or whole blood– which is called the IFN-signature [25]. IFNs are cytokines involved in viral immune responses, and three types of IFN are distinghuished. It has been shown that activation of the type-I IFN system correlates with disease activity and autoantibody levels – mainly anti-dsDNA and anti-Ro/SSA [26,27]. Interferon–α (IFN-α) belongs to type I IFNs and is an important player in the pathogenesis of SLE. This cytokine is mainly produced by plasmacytoid dendritic cells and forms a link between the innate and adaptive immune system by supporting differentiation, proliferation and survival of T- and B-cells. [28] Type-II IFN, which includes only IFN-γ, is also involved in pathogenesis of SLE, but the exact role has not been elucidated yet [29]. IFN-γ is increased in SLE and correlates with anti-dsDNA antibody levels [29]. This cytokine is mainly produced by effector natural killer-cells as part of the innate immune response, and by T-helper and cytotoxic T-cells as part of the antigen-driven adaptive immune response. IFN-γ, like IFN-α, induces production of B-cell activating factor (BAFF) [30]. It also plays an important role in T-cell differentiation and class switching from IgM to IgG production in B-cells. Notably, distinguishing IFN-type I and II inducible genes is not always unambiguous, as many genes can be induced by both IFN-types [31].

IFN-gene expression has been studied in iSLE. Li et al. compared IFN-inducible genes in whole blood of 24 iSLE-patients ($>$ 1 and $\leq$ 4 ACR criteria) with SLE patients [32]. Interestingly, expression levels of IFN-genes were increased not only in 87% of SLE patients, but also in 50% of iSLE patients, compared to a group of healthy controls. Besides, a significant positive correlation was found between IFN-gene expression and numbers of SLE criteria as well as ANA-titers. Our research group recently published a cross-sectional study that also showed that IFN signature (encoding genes that are induced

both by IFN type I and II) is present in half of iSLE patients [33]. Furthermore, IFN-gene expression correlated with the number of autoantibodies and was negatively correlated with serum complement (C3 and C4) levels. Myxovirus resistance protein A (MxA) is a GTPase, which is directly induced by IFN type I. This protein, measured in lysed whole blood, correlates strongly with IFN gene score and seems to be a good candidate for an easily applicable marker of IFN gene upregulation [33,34].

In 2018, a prospective study on 118 patients at risk of SLE was published, with the hypothesis that IFN-upregulation might be a predictive factor for disease progression [35]. The inclusion criteria were a positive ANA-titre, symptom duration $<$ 12 months, $\leq$ 1 clinical SLICC criterion and no use of antimalarials or immunosuppressive drugs. After one year, 16% of patients progressed to either SLE or primary Sjögren Syndrome (pSS). Indeed, these patients had significantly higher IFN scores at baseline than the non-progressors, which suggests a potential role for IFN as predictive biomarker in unclassified autoimmune disease. After multivariable logistic regression, a subset of IFN-inducible genes was independently associated with development of SLE or pSS. This IFN test yielded a positive predictive value of 35% and a negative predictive value of 98%.

Furthermore, IFN-related chemokines have been measured in pre-SLE serum samples obtained from a military cohort [36,37]. Remarkably, serum IFN-γ, interferon-γ induced protein 10 (IP-10), monokine induced by IFN-γ (MIG) and monocyte chemotactic protein-3 (MCP-3) were significantly increased $\geq$ 4 years before fulfilling SLE classification in comparison with controls. Notably, these IFN-type II related soluble mediators preceded IFN-type I activity, which was found to be significantly increased within 2 years before disease classification. Likewise, during prospective follow up of SLE relatives, IFN-mediated soluble mediators (MCP-3, MCP-1, MIP-1β) at baseline were all significantly higher in individuals who later developed SLE than the ones who did not [24].

In conclusion, increased IFN-type I and II activity can be present more than four years before the diagnosis of SLE. Increased IFN gene expression in patients at risk of SLE is associated with progression to SLE. However, importantly, the available evidence is based on studies with small sample sizes, so the results should be validated in larger follow up studies. Also, there is no standardized test for IFN-gene expression, nor for IFN-related mediators. Although outcomes of these tests in research studies are usually compared to healthy controls, comparability between different studies, as well as clinical applicability are insufficient. Still, IFN- type I and -II gene expression and related soluble mediators are worth investigating as possible predictive markers for progression to SLE.

Other cytokines and soluble mediators

In the previously mentioned military cohort, a multiplex assay was performed for 30 immune mediators in 84 SLE patients with available serum samples from the period before disease classification [38]. Soluble mediators involved in both innate and adaptive immunity were elevated more than three years prior to classification, including T-helper-associated cytokines interleukin (IL)–4, IL-5, as well as innate cytokines IL-6 and IL12p7 (the active heterodimer of IL-12). Conversely, transforming growth factor β (TGF-β), a regulatory cytokine with an inhibitory effect on B cells, was decreased. The number of elevated mediators increased towards SLE classification.

Furthermore, of the aforementioned prospective study in unaffected first- and second-degree relatives of SLE patients (n = 409), 52 soluble mediators were measured in plasma [24]. After a mean follow up of 6.4 years, 45 (11%) developed SLE. Progression to SLE was associated, along with certain IFN-related mediators that already have been mentioned, with higher baseline levels of BAFF and stem cell factor (SCF), which plays a role in hematopoiesis. Furthermore, lower baseline levels of TGF-β were associated with development of SLE.

Table 1
Overview of potential predictive markers for development of SLE.

Immune system part	Potential predictive markers	References
Auto-antibodies	Anti-dsDNA Ab	10, 14, 16, 17
	Anti-cardiolipin Ab	11
	Increasing IgG:IgM autoantibody ratio	20, 21, 23
	Increasing autoantibody diversity	16, 17, 24
Interferon	IFN-inducible gene expression	32, 33, 35
	MxA	33, 34
	IFN-gamma	24, 36, 37, 38
	IP-10	36, 37
	MIG	36, 37
	MCP-3	36, 37
Soluble mediators	IL-5	24, 38
	IL-6	24, 38
	BAFF	24
	TGF-β	24
	SCF	24
Complement system	Complement 3	10, 35
	Erythrocyte bound C4d	39–41
	B-lymphocyte bound C4d	39–41

Abbreviatons Anti-dsDNA anti-doublestranded DNA; Ab antibody; IFN interferon; MxA myxovirus resistance protein A; IP-10 Interferon-gamma induced protein 10; MIG monokine induced by IFN-γ; MCP monocyte chemotactic protein; IL interleukin; BAFF B-cell activating factor; TGF transforming growth factor; SCF stem cell factor.

In conclusion, these studies show that serum and plasma levels of various cytokines and chemokines involved in both innate and adaptive immunity can be altered up to many years before disease classification. Some could be indicative of progression to SLE, but more research is needed on this subject.

Complement system

Components of the complement pathway could be useful as biomarkers, since low levels of serum or plasma complement 3 (C3) and complement4 (C4) are an important feature of active SLE. Indeed, in a retrospective study of patients with 1–3 ACR criteria, decreased C3 levels occurred significantly more often in patients who later developed classified SLE (25%) than in patients with persisting iSLE (3%) [10]. However, this was a small sample size with only 8 subjects progressing to SLE. On the contrary, in the before mentioned prospective study of Yusof et al. about individuals at risk of an autoimmune disease, the complement levels were not associated with transition to established disease [35]. Notably, this study also had a limited number of SLE progressors (19 of 118). So the predictive role of complement depletion should be analyzed in more extensive prospective subject cohorts.

Combined predictive models and serological markers

In some of the above mentioned studies, multivariate analyses have been performed in order to construct predictive models for SLE classification.

Munroe et al. performed random forest modeling in the cohort of 509 SLE-relatives. They showed that, besides ACR criteria and self-reported symptoms at baseline, increased levels of SCF and decreased levels of TGF-β were most predictive of SLE development. The authors reported a negative predictive value $>$ 98% for this model and a positive predictive value of 51% [24].

The same research group performed random forest modeling in the study on IFN-related mediators in a military cohort and found that IFN-γ, MCP-3, and specific autoantibodies (directed against chromatin and spliceosomes), best predicted future SLE classification in one study [36]. In the same cohort, with measurement of different cytokines, a combination of ANA positivity, and increased levels of IL-5, IL-6, and MIG best identified future SLE patients, with a reported positive predictive value of 96%, and negative predictive value of 84%.

Complement bound to blood cells has been found to be of additional value in diagnosing SLE. Interestingly, combined testing of cell-bound

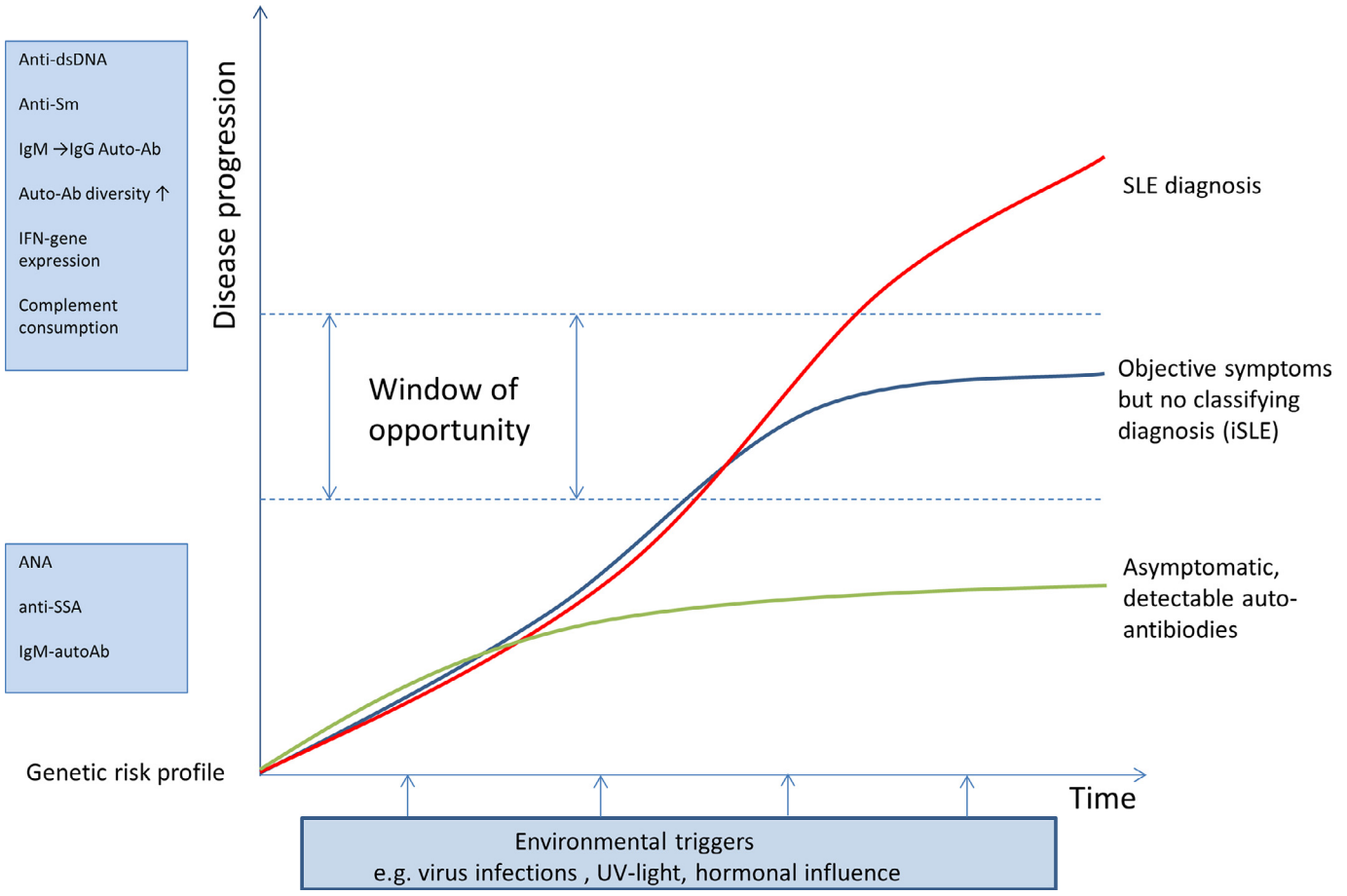

Fig. 1. Schematic timeline of the stages preceding SLE.
The phase of objective clinical symptoms, but without classifiable autoimmune disease, provides a window of opportunity for early intervention.
Abbreviations: ANA = antinuclear antibodies, Ab = antibody, IFN = interferon, anti-Sm = anti-Smith, anti-dsDNA = anti-doublestranded DNA, SLE -= systemic lupus erythematosus, iSLE = incomplete SLE.

complement activation in erythrocytes and B-lymphocytes, anti-dsDNA and auto-antibodies yielded sensitivity of 80% for SLE diagnosis [39–41]. Recently, a multianalyte assay panel was tested in 92 consecutive iSLE patients who fulfilled 3 ACR criteria, including erythrocyte bound C4d, B-lymphocyte bound C4d, ANA, anti-dsDNA, anti-Sm as well as other autoantibodies [42]. A validated multianalyte panel score based on the combination of all these tests was calculated [43]. At baseline, membrane-bound C4 was found in 28% of these patients compared with 61% of SLE controls, and was present more frequently than anti-dsDNA and serum complement depletion. During 9–18 months follow up of 68 iSLE patients, 20 (29%) transitioned to SLE as classified by ACR criteria. These patients significantly more often had increased multianalyte assay scores (40%) than the non-progressors (17%). Thus, cell-bound complement activation might be of additional value in predicting transition to SLE. However, in total, 16 subjects had a positive multianalyte assay score at baseline, 8 of which progressed to SLE, resulting in a positive predictive value of 50%. Unfortunately, membrane-bound C4 is tested by quantitative flow cytometry, which is not easily applicable in daily clinical practice.

Conclusion and recommendation

Early recognition of SLE is important in order to start treatment before organ damage develops. Fig. 1 provides a schematic overview of the stages preceding SLE. Although many studies have been performed on preclinical SLE and incomplete SLE, the results are not generalizable, because of limited sample sizes of the study cohorts. Consequently, there are no accurate and well defined predictive tests with known cut-off values available yet that can identify individuals at high risk of transitioning to SLE. Another puzzler is the heterogeneity of the patient groups, regarding clinical and immunologic manifestations. Therefore, there is a strong need for prospective studies on larger cohorts of iSLE patients.

Nonetheless, based on the available data, some immune mediators in particular might help predict progression to SLE (see table 1.)

Increased expression of IFN-type I inducible genes, high autoantibody diversity, increased IgG:IgM autoantibody ratio, presence of anti-dsDNA and anticardiolipin antibodies, as well as membrane-bound complement are all associated with progression to SLE. Also, some cytokines seem to have predictive value, especially when used in combination with other factors.

Unfortunately, many of the mentioned tests are not (yet) part of routine clinical testing and no cut-off values are avalaible for prediction of progression from SLE to iSLE. At this moment, besides clinically monitoring, we therefore suggest repeated testing of ANA, anti-dsDNA and screening of other extractable nuclear antigen antibodies (ENA), as well as serum concentrations of C3 and C4, for risk estimation of patients with iSLE in clinical practice. Increasing ENA-titers and ENA-diversity, and decreasing complement levels could be predictive for progression to SLE. More frequent follow-up is indicated when one or more of these changes occur. If applicable, IP-10, an IFN-related marker, could be added to these measurements in daily clinical practice, as it is easily tested by ELISA and may contribute to predicting progression to SLE.

Furthermore, in a research setting, many mediators are of interest, namely IFN-related chemokines, BAFF, SCF, and TGF-β. Also, IgG:IgM

autoantibody ratio could help identify progression to SLE. Importantly, these biomarkers should be tested in a large longitudinal cohort of well characterized patients at risk of developing SLE to be able to calculate positive and negative predictive values for progression to SLE.

Ideally, combining the best predictive biomarkers from these large prospective cohorts will result in better prediction of disease outcome in patients with iSLE.

Statements

Declaration of Competing Interest

The authors have no conflict of interest

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