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Preclinical SLE

Julie M. Robertson, PhD¹ and **Judith A. James, MD, PhD^{1,2}**

¹Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

²Department of Medicine, University of Oklahoma Health Sciences Center, 1200 N. Phillips Ave, Oklahoma City, OK, USA, 73104

³Department of Pathology, University of Oklahoma Health Sciences Center, 1200 N. Phillips Ave, Oklahoma City, OK, USA, 73104

⁴Oklahoma Clinical and Translational Science Institute, University of Oklahoma Health Sciences Center, 1000 N. Lincoln Blvd, Suite 2100, Oklahoma City, OK, USA, 73104

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Introduction

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease featuring multiple organ system involvement and the presence of autoantibodies. The numerous variations of clinical symptom presentation often make diagnosis difficult. The current American College of Rheumatology (ACR) criteria for the classification (not diagnosis) of SLE requires that patients must meet a minimum of 4 out of 11 defined clinical and/or serologic criteria.^(1, 2) In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group developed and proposed new classification criteria, which require at least one clinical and one serologic criterion to be met and allows disease classification based upon the presence of 4 out of 17 criteria (Figure 1).⁽³⁾ However, clinical diagnosis of SLE is a distinct challenge from that of its classification for clinical studies and trials. As SLE is a heterogeneous disorder, a large number of individuals present with clinical symptoms of SLE, but do not meet disease classification criteria. Due to the variety of possible clinical symptoms, individuals can wait years for a diagnosis while ongoing inflammatory processes cause irreversible organ damage.

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Corresponding author: Judith A. James, MD, PhD, Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, OK 73104, Phone: (405) 271-4987, Fax: (405) 271-7063, Judith-James@omrf.org.

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Preclinical lupus thus encompasses a broad range of individuals, including individuals with enhanced genetic risk for SLE development without current clinical symptoms to individuals with autoantibodies and some clinical features of SLE that do not meet ACR disease classification criteria.⁽⁴⁾ This period before SLE disease classification has, over the years, been categorized as “latent lupus”⁽⁵⁾ or “incomplete lupus”.⁽⁶⁾ Latent lupus identifies a group of individuals with features consistent with SLE which meet one or two of the 1971 or 1982 classification criteria along with the presence of minor criteria such as fever, fatigue, low complement, or lymphadenopathy.⁽⁵⁾ Incomplete lupus (ILE) refers to individuals with fewer than four of the ACR SLE classification criteria.⁽⁶⁾ Additionally, “undifferentiated connective tissue disease” (UCTD) is a broader term referring to individuals with clinical symptom manifestations suggestive of a specific connective tissue disease without meeting disease classification criteria.⁽⁷⁾ The UCTD group does contain a subset of individuals that may transition to SLE. This chapter will examine preclinical lupus spanning the period of time before SLE classification with particular attention to the time between serologic or cellular evidence of autoimmunity and SLE diagnosis (Figure 2, see ⁽⁵⁻¹⁰⁾ for more information). Additionally, studies are discussed which examine individuals who transition to SLE from UCTD, from ILE, or from previously healthy mothers of neonatal lupus or congenital heart block children.

Significance of autoantibodies in preclinical SLE

Autoantibodies are a hallmark SLE characteristic. Despite the variability of clinical symptoms, the vast majority of newly diagnosed lupus patients have detectable autoantibodies. Through a partnership with the United States military rheumatologists and the United States Department of Defense Serum Repository (DoDSR), a large sample repository comprised of longitudinal blood samples and basic laboratory evaluations obtained upon entry into the military and throughout their military service. These samples span the timeframe before clinical disease to at or after SLE diagnosis and provide a unique resource to examine serologic features of preclinical SLE. Using serial serum samples (n=633) from 130 patients who subsequently developed SLE while in the US military, 115 (88%) of the SLE p were found to have at least one autoantibody present in a pre-diagnosis serum sample. In some cases, this initial autoantibody was present up to 9.4 years (mean 3.3 years) before SLE classification. Anti-nuclear, anti-phospholipid, anti-Ro, and anti-La antibodies were present significantly earlier (mean=3.2 years) than anti-Sm and anti-nRNP antibodies (1.2 years) (P=0.005). Anti-dsDNA antibodies appeared, on average 2.2 years before diagnosis, while anti-ribosomal P and anti-C1q antibodies were detectable on average 1.1 and 1.4 years before classification, respectively.^(11, 12) Of the patients who had at least two positive samples, one within 6 months of clinical SLE diagnosis and the second more than 6 months before diagnosis (N=26), 73% (n=19) had increases in their anti-dsDNA antibody levels as they moved toward diagnosis (mean= 227 units; S.E.M. =37 units vs mean=743 units, S.E.M.=212 units, p=0.018).⁽¹³⁾ As such, autoantibodies are routinely observed to be present before SLE classification and display an increase in antibody specificity number and levels leading up to diagnosis.

Utilizing a multiplexed, bead-based method to test for the presence of autoantibodies directed against the specific protein antigens 60kd Ro, 52kd Ro, La, Sm/nRNP, nRNP, nRNP

70K, nRNP A, histones, dsDNA, and ribosomal P, 33 of 114 patients (25%) initially had a single, detectable autoantibody specificity and others had multiple specificities in their first autoantibody-positive sample prior to SLE diagnosis.⁽¹⁴⁾ The most common initial antibody recognized was anti-60kD Ro with anti-nRNP A, anti-dsDNA, and anti-La antibodies being the next most common single, initial autoantibodies.⁽¹²⁾ Protein targets within linked autoantibody subsets were commonly targeted first, such as nRNP A before or with nRNP 70K or 60kD Ro before or with 52kD Ro. Other protein targets occurred with almost equal frequency, commonly simultaneous or closer together than we could assess with DoDSR samples. Understanding these early autoantibody responses may provide keys to understanding the targets and mechanisms of initial breaks in tolerance in SLE that can, in turn, be developed into robust early diagnostic markers or tolerogens of early disease.

Some patients with anti-phospholipid antibody syndrome subsequently develop clinical SLE.⁽¹⁵⁻¹⁷⁾ Sera from the DoDSR were used to evaluate the temporal relationship between aPL antibodies and clinical SLE classification.⁽¹⁸⁾ A total of 24 cases (18.5%) were positive for IgG and/or IgM aPL antibodies prior to SLE. Anti-cardiolipin (aCL), appeared, on average, 3.0 years before SLE classification. In addition, the presence of aCL before clinical classification was associated with a broader disease presentation. These patients eventually met an average of 6.1 (of the 11) 1997 SLE classification criteria, compared with 4.9 criteria for other patients ($p < 0.001$). The early aCL-positive population also had more frequent renal disease, CNS disease, thrombocytopenia and clotting events. In this population, aCL preceded initial thrombotic events by a mean of 3.1 years.⁽¹⁸⁾

Several studies have indicated that autoantibody specificities are associated with disease manifestations of SLE and may be able to predict the development of these clinical features. Within the DoDSR military cohort, one of the most common early clinical symptoms of SLE was arthritis, as such stored samples from SLE patients were analyzed for IgG rheumatoid factor (RF) to determine whether RF preceded arthritis onset. Of the 130 patients in the DoDSR, 17 (13%) were found to have RF, present on average 2.1 years before the first documented arthritis symptom and 16 of the 17 RF-positive patients eventually developed inflammatory arthritis. Anti-dsDNA responses have been associated with the presence of renal disease. Of the 80 patients with anti-dsDNA positive samples, 38 (48%) developed ACR-defined renal disease with 35 of them having detectable antibodies against dsDNA before or concurrently with renal disease onset.⁽¹²⁾ These data further support the associations between select lupus-specific autoantibodies and specific disease symptoms; however, how the concentration, specificity and affinity of these autoantibodies change during the preclinical period is unknown. Taken together, these studies show that autoantibodies are detected years prior to SLE disease diagnosis.^(4, 11-13, 18)

Serologic Markers observed in a Swedish SLE cohort prior to SLE diagnosis

Serological biomarkers were examined in a Swedish retrospective cohort similar to the DoDSR. Both retrospective cohorts have samples prior to and at SLE diagnosis and have had extensive characterization along with medical record abstraction. However, the Swedish cohort contains only one sample collected prior to SLE diagnosis, while the DoDSR has, on average, 3.6 samples collected and studied prior to disease classification. Additionally, the

Swedish cohort has 19 individuals enrolled from a pregnancy cohort and contains a mixture of serum and plasma samples which cannot be directly compared to each other for other serologic biomarkers, such as cytokines and chemokines. In contrast, the DoDSR only contains serum samples and has no pregnant individuals enrolled in the cohort.

SLE patients seen at the Department of Rheumatology at the University Hospital in Umeå, Sweden were enrolled, examined, and donated a blood sample.⁽¹⁹⁾ Thirty eight of these individuals were found to have donated a sample prior to SLE disease classification. Despite the lack of numerous pre-disease samples, the Swedish cohort is still a rich source of preclinical SLE information. In the Eriksson et al. 2011 article, ANA were detected in 63% of individuals that later transition to SLE, on average, 5.6 ± 4.7 years prior to onset of clinical symptoms.⁽¹⁹⁾ Anti-Ro antibodies were observed first 6.6 ± 2.5 years prior to clinical symptom presentation and 8.1 ± 2.3 years prior to SLE classification. Anti-RNP and anti-histone antibodies were also observed early at 5.9 ± 2.5 and 5.0 ± 1.5 years prior to clinical symptoms. Anti-Sm and anti-centromere antibodies were observed closer to disease classification at 1.4 ± 0.6 years prior to SLE classification.⁽¹⁹⁾ The number of autoantibodies in preclinical SLE individuals increased after first clinical symptom from 1.4 to 3.1 ($p < 0.0005$). Similar to what was seen in the DoDSR cohort, autoantibodies were also associated with specific disease manifestations. For example, in preclinical individuals with serositis, the average number of autoantibodies was higher than individuals presenting with arthritis and skin manifestations (2.5 autoantibodies and 1.7 autoantibodies for arthritis, and 0.9 autoantibodies for skin manifestations of SLE).⁽¹⁹⁾ Additionally, the autoantibodies observed in individuals with serositis appeared closer to diagnosis (1.9 years prior to diagnosis) than in individuals with arthritis (6.7 years prior to diagnosis) or skin manifestations (4.2 years prior to diagnosis).⁽¹⁹⁾

In another study by Eriksson et al., samples from the Swedish patient group were examined for alterations in cytokines and chemokines between pre-disease samples and samples collected following SLE diagnosis.⁽²⁰⁾ Here, samples from 35 SLE patients and 140 healthy controls were examined for chemokines and cytokines and their relationship to previously detected autoantibodies.⁽²⁰⁾ Increased levels of IP-10 (interferon gamma induced protein 10) were observed more frequently in pre-disease time points than in the healthy controls ($p = 0.02$). Concentrations of IFN- α (interferon- α) and IP-10 were significantly higher among autoantibody positive samples than autoantibody negative pre-diagnosis samples or controls. Specifically, IP-10 levels were increased in individuals positive for ANA, anti-Ro, and anti-Jo1. IFN- α levels were increased in individuals positive for anti-La responses. IL-10 levels were higher in anti-RNP positive individuals. On the other hand, MCP-1 (monocyte chemotactic protein 1) levels were significantly decreased in anti-Ro and anti-La positive individuals compared to samples from anti-Ro and anti-La negative individuals and controls.⁽²⁰⁾ This study shows that like autoantibodies, cytokines and chemokines are altered prior to SLE diagnosis.

While this study provides valuable information on the alterations of cytokines prior to SLE diagnosis it does have limitations. Half of the samples used for cytokine analysis were plasma while the samples obtained through the maternity cohort were sera. These two sample types are difficult to directly compare as biomarkers in serum often have a shorter

half-life than the same biomarkers in plasma. Additionally, many studies have shown that during pregnancy, the immune system of the mother is altered⁽²¹⁻³⁰⁾, as such the cytokine alterations observed could be influenced by the pregnancy itself rather than the preclinical features of SLE. Further studies are required to elucidate alterations in soluble mediators during preclinical phases of SLE.

While there is a lack of studies examining autoantibody and cytokine or chemokine biomarkers in preclinical periods of SLE, these studies suggest that altered biomarkers may also be critical during preclinical periods of SLE, as well as in otherwise healthy ANA positive individuals. Larger studies of ethnically diverse lupus patients are needed to confirm and expand these initial findings and to elucidate the mechanisms responsible for the altered serological biomarkers.

Transition from Incomplete to Classified SLE

Incomplete lupus erythematosus (ILE) is a term used to refer to individuals with clinical symptoms indicative of SLE but who have fewer than four 1997 ACR classification criteria. Several studies have followed groups of ILE patients to evaluate and identify predictors of transition to SLE and to further elucidate preclinical features of SLE. In a 1989 paper, 38 ILE patients (defined as meeting up to three ACR SLE classification criteria) were followed for an average of 1.6 years with only 2 individuals transitioning to SLE.⁽⁶⁾ The Dallas Regional Autoimmune Disease Registry (DRADR) enrolls autoimmune disease patients, first-degree relatives of autoimmune disease patients, and healthy controls. In this retrospective study cohort, 15 individuals out of 124 were classified as ILE and 99 out of 124 were classified as SLE.⁽³¹⁾ The ILE patients were shown to have a significantly lower mean damage score than SLE patients (0.67 ± 0.32 vs 1.67 ± 0.17 ; $p=0.036$) and a significantly shorter disease duration (4.33 ± 0.94 years vs 10.24 ± 0.75 years; $p=0.003$).⁽³¹⁾ In another US-based study from the DRADR following 22 ILE Patients (<4 ACR criteria) for an average of 2.4 years, 14% ($n=3$) transitioned to SLE classification.⁽³²⁾ All patients who transitioned were female, of younger age, and showed increases in IgG autoreactivity. These transition individuals were more likely to have autoantibodies against proliferating cell nuclear antigen, $\beta 2$ microglobulin, C1q, and hemocyanin at baseline compared to those who remained ILE. A quantitative risk score was generated to identify individuals that would transition to SLE. This risk score, comprised of female gender, baseline ANA ELISA >200 units, baseline age < 40, increase in overall IgG autoreactivity on an autoantigen array, and presence of IgG responses against seven baseline autoantigens, showed strong differentiation between ILE patients who transitioned to SLE classification compared to those which remained ILE ($p = 1.38 \times 10^7$).⁽³²⁾

In another study utilizing SLE patients ($n=73$), ILE patients ($n=43$), unaffected false discovery rate controls ($n=32$), and healthy controls ($n=28$) from the DRADR, ILE and SLE patients had similar mean ANA levels ($p>0.05$) that were significantly higher than FDRs ($p<0.001$) and healthy controls ($p = 0.5$).⁽³³⁾ In examining differences in autoantibody response to autoantigens between ILE and SLE patients, elevated levels of at least one IgG autoantibody were detected in 19% of ILE patients compared to 26% of SLE. Additionally,

the IgG to IgM autoantibody ratios showed a stepwise increase from healthy controls to ILE to SLE in this study.⁽³⁴⁾

A study from Puerto Rico followed 87 patients who met at least one ACR clinical SLE criterion for a mean of 2.2 years. Eight individuals transitioned to SLE in the follow-up period. Those patients who evolved to SLE were more likely to have photosensitivity, malar rash, oral ulcerations, anti-dsDNA responses, and low levels of C3.⁽³⁵⁾ A collaborative study of 122 patients with ILE (diagnosed less than one year) followed 100 patients who did not transition to SLE for at least three years. These longterm ILE individuals had common baseline clinical symptoms of leukopenia, fatigue, arthritis, and mucocutaneous involvement.⁽³⁶⁾ In a Swedish study with 28 ILE patients (<4 ACR criteria) followed on average of 5.3 years, malar rash, aCL, and thrombocytopenia were enriched in the 16 individuals who transitioned to SLE classification.⁽³⁷⁾

When examining a small group of SLE patients (n=27), ILE patients (n=24), unaffected first-degree relatives (n=22) and unaffected, unrelated healthy controls (n=11), Li et al examined differences in interferon genes. A set of 63 interferon genes were upregulated in 83% of SLE patients but only in 50% of ILE patients, compared to no interferon high individuals in the two control groups. Interferon high status was shown to be associated with IgG autoantibody responses primarily targeted against DNA or RNA-binding proteins, in both SLE patients and ILE patients. Additional longitudinal evaluation of ILE patients, both in the interferon-high and interferon-low groups, are necessary to see if ILE patients with elevated interferon signatures are at higher risk of transition to SLE.⁽³⁸⁾

In the above studies, that the ILE individuals who transitioned to SLE classification had relatively mild SLE without major organ involvement (Table 1). In total, approximately 10% of ILE patients will transition to SLE oftentimes with a disease course that lacks nephritis, vasculitis or major CNS involvement. Because ILE describes the time period with some SLE symptoms leading up to SLE diagnosis, all SLE patients may have a period of ILE; however, only those individuals that do not transition to or have delayed transition to SLE are typically identified as having ILE. Further studies are needed to assess whether ILE is a different disease or a milder form of SLE, as well as to decipher mechanisms by which only approximately 10% of ILE patients may transition to SLE.

Transition from undifferentiated connective tissue disease to SLE

Individuals with UCTD demonstrate clinical symptoms indicative of autoimmune connective tissue disease such as SLE, Sjögren's syndrome (SS), or rheumatoid arthritis; however, these individuals do not meet clinical classification criteria. Although up to one third of individuals with UCTD transition to a disease diagnosis^(39, 40), the remaining individuals do not. Studies investigating clinical and serological features of UCTD have begun to provide knowledge on preclinical features of disease.

In a 1991 multi-institutional cohort study of 213 US-based early UCTD patients (within 1 year of identification) investigated factors that were predictive of SLE onset. After 5 years of follow-up, 8.5% of the cohort (n=18) transitioned to SLE.⁽⁴¹⁾ A univariate analysis indicated that individuals more likely to transition to SLE were younger and African-

American. The transition individuals also displayed alopecia, serositis, discoid lesions, anti-dsDNA, anti-Sm, positive ANA with a homogeneous pattern, Coombs' positivity or a false-positive syphilis test. After regression modeling, discoid lesions, serositis, anti-Sm (by precipitin), or ANA-homogenous patterns remained the best predictors of transition to SLE in these UCTD subjects.⁽⁴¹⁾

In a study from Italy, 84 patients with early UCTD (symptoms onset within the past year) were followed for five years.⁽⁴²⁾ Baseline characteristics of these individuals included Raynaud's (54%), arthralgias (51%), arthritis (23%), fever (23%) and weakness (16%). Thirty-three patients (39%) developed a defined CTD, including 7 patients with SLE (8.3% of the cohort). Univariate analysis showed anti-dsDNA, aCL, and fever correlating with subsequent SLE disease classification. aCL responses were not significant in the multivariate analysis.⁽⁴²⁾ Another study of UCTD patients (at least one clinical feature and autoantibody positive) were reported on one year⁽⁴³⁾ and five years⁽⁴⁴⁾ of follow-up. After five years, 18 of these patients had transitioned to SLE (22%). The presence of aCL responses and multiple autoantibody specificities were associated with subsequent SLE classification. In another study from Milano (Italy), 148 patients with UCTD were retrospectively evaluated. Of these, 36 developed a well-defined CTD after, on average, 4.5 years of follow-up. Anti-dsDNA responses were found to predict the evolution from UCTD to SLE classification.⁽⁴⁵⁾

A large group of UCTD patients (n=665) were followed in Hungary between 1994 and 1999.⁽⁴⁶⁾ Of these 665 individuals, 230 developed a defined CTD, including 28 with SLE. Fever, serositis, photosensitivity, ANA homogenous pattern, and dsDNA antibodies associated with the development of SLE. SLE patients with a documented UCTD period were more likely to be older, have more serositis, less skin rash, less renal involvement and less hemolytic anemia compared to SLE patients without a documented UCTD period.⁽⁴⁶⁾ In a study from Portugal, 74 out of the 184 UCTD patients presented with a lupus-like disease (based upon clinical features and autoantibody profiles)⁽⁴⁷⁾; however, longer-term follow-up of these individuals are not readily available. Nonetheless, in this cohort, arthralgia and arthritis were the most common symptoms with 40% of the study participants showing lupus-like symptoms with a higher frequency of arthritis, cytopenia, oral ulcers, and dsDNA antibodies compared to other UCTD individuals in the cohort.⁽⁴⁷⁾ The presence of anti-dsDNA antibodies in the UCTD individuals with lupus-like disease was associated with decreased levels of C3 and C4, while aCL was associated with thrombocytosis.⁽⁴⁷⁾ Finally, a study from the Netherlands followed 65 ANA positive individuals (excluding anti-dsDNA antibody positive individuals) referred for rheumatology evaluation. Of these 65 individuals, a specific rheumatic disease diagnosis could be established in 38 within the 2 years of follow-up, including 6 who transitioned to SLE after a median of 2.2 years.⁽⁴⁸⁾

Several studies have examined cellular and serological differences in individuals with UCTD in hopes of further identifying UCTD individuals that transition to a defined connective tissue disease. In examining the cellular differences between UCTD individuals who do and do not transition to defined disease along with healthy controls, individuals with UCTD have elevated numbers and percentages of activated T cells, memory T cells and natural killer T cells than healthy, unaffected controls.⁽⁴⁹⁾ In UCTD individuals who

transition to defined disease, the percentages of CD4+ IFN- γ + T-helper 1 cells here higher than controls and UCTD individuals who do not transition to disease. Additionally, the percentage and number of CD4+CD25+ Foxp3+ natural regulatory T cells were diminished in UCTD individuals compared to healthy controls.⁽⁴⁹⁾ When vitamin D levels were examined in a collection of 161 UCTD individuals, 50 UCTD subjects demonstrated significantly lower levels of vitamin D in both summer and winter compared to controls ($p=0.01$ and $p=0.0001$, respectively).⁽⁵⁰⁾ Clinical symptoms of photosensitivity, erythema, and discoid rash were associated with low vitamin D levels in the UCTD patients. Additionally, autoantibodies against RNP, Ro, and CCP were associated with low vitamin D levels in UCTD patients.⁽⁵⁰⁾ Importantly, Zold et al showed that the UCTD patients with the lowest vitamin D levels were the ones who tended to transition to a defined connective tissue disease⁽⁵⁰⁾ and that low vitamin D levels in UCTD patients impaired regulatory T-cell homeostasis.⁽⁵¹⁾

Although most of the UCTD patients remain within the UCTD category, preclinical lupus information can be gleaned from the cumulative transition across these studies of 93 individuals to SLE diagnosis. UCTD individuals with multiple autoreactivities, ANA-homogeneous pattern, dsDNA antibodies, Sm antibodies, and aCL responses are at higher risk for transitioning to SLE, as are individuals with multiple lupus-like clinical features (Table 2). Patients who remain in the UCTD group tend to have a mild clinical picture with little to no major organ involvement, arthralgias, arthritis, Raynaud's phenomenon, and leucopenia.^(40, 52) Please see reviews^(40, 53, 54) for more detailed information.

Transition of neonatal lupus erythematosus/congenital heart block patient mothers to SLE

The Research Registry for Neonatal Lupus was created to help study the disease evolution of the mothers of and the neonates with neonatal lupus erythematosus (NLE). This rich resource started in 1994 collects diagnostic information on enrolled mothers and their children affected with congenital heart block (CHB) or NLE. Importantly, in terms of evolution of SLE, a study utilizing this resource has examined rheumatic disease progression in mothers of neonates with NLE. Here, 387 NLE children and 321 anti-Ro antibody positive mothers were assessed.⁽⁵⁵⁾ Among the mothers of neonates with NLE, 51 were asymptomatic (no clinical symptoms of rheumatic disease), 20 pauci-UAS (undifferentiated autoimmune syndrome with up to 2 of arthralgias, oral or nasal ulcers, photosensitivity, lymphopenia, Raynaud's phenomenon, dry eyes or dry mouth, of parotid enlargement), 12 poly-UAS (present with more than two of the Pauci-UAS symptoms), 12 probable SS (at least 2 of dry eyes, dry mouth, or parotid enlargement), 6 SS (met the revised European classification of SS), 10 SLE (met 4 or more ACR SLE classification criteria), and 11 with SLE and SS. In mothers that were asymptomatic at enrollment ($n=51$), 49% remained asymptomatic up to a mean 4.1 years of follow-up. Thus, the presence of NLE in the neonate does not directly associate with the development of SLE in the mothers.⁽⁵⁵⁾ Additionally, mothers with only anti-Ro antibodies were more likely to remain asymptomatic, while mothers with both anti-Ro and anti-La antibodies were 1.8 times more likely to develop a rheumatic disease.⁽⁵⁵⁾

Future considerations

Preclinical lupus is a broad concept that seeks to categorize a wide range of individuals including those with increased genetic risk of developing SLE but no clinical symptoms nor positive standard lupus serology tests to individuals with autoantibodies and clinical features consistent with SLE but who do not meet the current ACR SLE classification criteria. In addition, there is some debate over what time frame preclinical lupus encompasses. Some have argued that preclinical lupus should focus on the time period between evidence of immune dysregulation to before the first clinical feature in an individual who eventually will be diagnosed with SLE. On the other hand, others have identified the preclinical SLE phase as the entire clinically asymptomatic period leading up to SLE classification. Due to the variation between these two definitions, a number of terms have been proposed to describe this preclinical period such as latent lupus⁽⁵⁾, incomplete lupus⁽⁶⁾, lupus-like or probable lupus.⁽⁵⁶⁾ Additionally, the more broader term of UCTD, which identifies individuals with clinical symptoms suggestive of a connective tissue disease, has also been used to identify preclinical SLE patients; however, UCTD also encompasses individuals that develop non-SLE connective tissue disease such as SS or systemic sclerosis. Clearly more studies are needed in order to better classify individuals with preclinical lupus. These studies can be used to create a consensus on preclinical lupus terminology as well as to help understand and investigate early SLE natural history.

Studying preclinical lupus may also lead to several potential benefits (please see Box 1 for a partial list). Individuals in the preclinical phase of disease are often not on immunosuppressive medications. This allows for a clearer picture of early disease events without the confounding effects of medications, irreversible or severe organ damage, or ongoing aggressive inflammation. In addition, studying patients during preclinical or early clinical stages can identify individuals at increased risk for full SLE development or for severe SLE complications that can lead to the potential of early intervention. These studies can also lead to improved understandings of specific etiologic factors of SLE, such as environmental or epigenetic triggers of disease development, as well as the earliest events in lupus autoimmunity allowing for improved diagnostic tools, identification of biomarkers of early disease activity, and elucidating novel pathways for therapeutic development.

Early identification of individuals at high-risk for development of clinically apparent disease or who have early mild clinical disease will allow for closer monitoring and early treatment to reduce or inhibit major organ involvement in SLE. Early intervention would also allow for the modulation of the dysregulated immune and inflammatory responses, thus reducing morbidity and early mortality. Therefore, the preclinical study of SLE along with additional longitudinal cohorts is poised to develop prospective studies to assess immune parameters and other serologic responses of disease onset and to understand mechanisms of disease to drive directed therapeutic development and create potential prevention trials. A retrospective analysis of individuals in the DoDSR suggested that early intervention with hydroxychloroquine (HCQ) and/or prednisone may delay disease onset and slow accrual of autoantibody specificities.⁽⁵⁷⁾ In this study individuals treated with HCQ prior to diagnosis had a longer time between the onset of the first clinical symptom and SLE classification than matched, HCQ-untreated SLE patients (median times of 1.08 versus 0.29 years,

respectively, $p=0.018$). Patients treated with prednisone prior to SLE classification progressed more slowly to ACR classification criteria than matched prednisone-untreated SLE patients ($p=0.011$). Additionally, individuals receiving both HCQ and prednisone ($n=13$) had a significantly longer time between initial clinical symptoms and SLE classification than individuals treated with only prednisone ($n=14$) before diagnosis ($p=0.03$). Importantly, patients treated with HCQ had a lower rate of autoantibody accumulation and decreased numbers of autoantibody specificities at and after SLE diagnosis.⁽⁵⁷⁾ These findings indicate that preventative treatment in individuals at increased risk of SLE development may be beneficial and a preclinical study of HCQ in high-risk individuals for subsequent disease development is warranted.

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Synopsis

Preclinical lupus encompasses a broad range, spanning from individuals with enhanced risk for SLE development without current clinical symptoms to individuals with autoantibodies and some clinical features of SLE that do not meet ACR disease classification criteria. Studies have identified antibody and serological biomarkers present years before disease diagnosis. Incomplete lupus (ILE) and undifferentiated connective tissue disease (UCTD) also fall under the preclinical periods of disease. Interestingly, only 10-20% of these individuals transition to SLE and many have a mild clinical disease course with little renal or nervous system involvement. Further studies into preclinical lupus are warranted to characterize biomarkers of early disease, to identify individuals in need of close monitoring or preventive intervention, and to elucidate mechanisms of disease without the confounding factors of immunosuppressive medication and advanced tissue or organ damage.

Key Points

- Autoantibodies are present and cytokine biomarkers are altered prior to SLE diagnosis.
- ILE patients who transitioned to SLE classification oftentimes have mild SLE without major, life-threatening organ involvement.
- UCTD individuals with multiple autoreactivities, ANA-homogeneous pattern, anti-dsDNA, anti-Sm, and aCL responses are at higher risk for transitioning to SLE.
- New classification schemes are needed to adequately capture all phases of SLE.
- New preclinical lupus studies are warranted to elucidate mechanisms of disease progression without the confines of advance organ/tissue damage and immunosuppressive medication.

Box 1. Reasons for studying preclinical SLE

1. Understand disease pathogenesis without confounding effects of concurrent medication or extensive, irreversible disease damage
2. Identify at risk individuals to allow for close monitoring and implementation early interventions to delay disease progression and damage
3. Characterize biomarkers of early disease for the development of early screening tests and improved diagnostic tools.
4. Create prevention studies to assess effectiveness of preventative treatment in high risk individuals

Figure 1.
Systemic Lupus International Collaborating Clinics (SLICC) proposed new SLE classification criteria.

Figure 2.
Proposed stages of lupus autoimmunity development.

Table 1

Summary table of studies with patients who transitioned to SLE from ILE.

Year	Reference ()	Patient Population	No. Transition To SLE (%)	Predictors of Transition	Years F/U
1989	Ganczarczyk, et al ⁽⁵⁾	Latent lupus (1-2 ARA criteria, 71 or 82), additional minor criteria	7 of 22 (31.8%)	No Predictors	8 years (5-15 years)
1989	Greer, et al ⁽⁶⁾	ILE	2 of 38 (5.3%)	No Predictors	1.6 years
2000	Vila, et al ⁽³⁵⁾	ILE	8 of 87 (9.2%)	Photosensitivity, malar rash, oral ulcers, low C3 levels, and anti-dsDNA antibodies	2.2 years
2004	Ståhl Hallengren, et al ⁽³⁷⁾	ILE (positive ANA and at least one 1 ACR clinical criterion)	16 of 28 (57.1%)	Malar rash and anti-cardiolipin antibodies	5.3 years (1-10 years)
2010	Lastrup, et al ⁽³⁸⁾	ILE	7 of 26 (26.9%)	Mild disease, absence of renal and CNS involvement	8 years (1-8 years)
2012	Olsen, et al ⁽³²⁾	ILE	3 of 22 (14%)	Female, young age, increased levels of IgG, antibodies against β 2 microglobulin, C1q, and hemocyanin	2.4 years

F/U = follow-up; ILE= incomplete lupus; CNS = central nervous system.

Table 2
Summary table of studies with patients who transitioned to SLE from UCTD

Year	Reference ()	Patient Population	No. Transition To SLE (%)	Predictors of Transition	Years F/U
1996	Calvo-Alen, et al ⁽⁴¹⁾	Started with 213 eUCTD (symptoms less than 1 year) and had complete 5 year data on 143	18 of 143 (12.6%)	Predictors: discoid lupus, serositis, ANA homogeneous, and anti-Sm by precipitation	5 years (1-5 years)
1998	Danieli, et al ⁽⁴²⁾	eUCTD, 84 patients	7 of 33 (21.2%)	Fever and anti-DNA antibodies	5 years (1-5 years)
1998	Mosca, et al ⁽⁴³⁾	UCTD (one autoantibody and one clinical feature)	12 of 91 (13.2%)	Multiple autoantibodies; less sicca Raynaud's and photosensitivity	3 years (1-8 years)
2000	Belfiore, et al ⁽⁵⁹⁾	UCTD	5 of 57 (8.77%)	Anti-60kD alone associated with transition	5 years (1-23 y)
2001	Cavazzana, et al ⁽⁴⁵⁾	UCTD (retrospective study)	45 of 148 (30.4%)	Anti-dsDNA antibodies	5 years (1-9 years)
2003	Bodolay, et al ⁽⁴⁶⁾	UCTD	28 of 665 (4.2%)	Fever, serositis, photosensitivity, ANA homogenous pattern, anti-dsDNA antibodies	5 years

F/U = follow-up; UCTD = undifferentiated connective tissue disease; eUCTD = early undifferentiated connective tissue disease.