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Evaluation of Progression From Preclinical to Systemic Autoimmune Rheumatic Disease: Novel Use of the European Alliance of Associations for Rheumatology/ American College of Rheumatology Systemic Lupus Erythematosus Classification Criteria as an Outcome Measure

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Objective. Our objective was to evaluate the development of a systemic autoimmune rheumatic disease (SARD) in undifferentiated and asymptomatic individuals with antinuclear antibodies (ANAs). We comparatively evaluated those who did and did not develop a SARD and fulfillment of classification criteria.

Methods. We conducted a cohort study of undifferentiated and asymptomatic patients with ANAs who were assessed for the development of a SARD. The primary outcome was a diagnosis of a SARD over a two-year period. We assessed fulfillment of classification criteria. Risk ratios (RRs) were used to evaluate differences among those who did and did not progress to a SARD.

Results. We evaluated 207 asymptomatic ANA-positive or undifferentiated patients, of whom 23 (11%) progressed to a SARD, whereas 187 (89%) did not progress. Progressors developed systemic lupus erythematosus (SLE) (n = 11 [48%]), Sjögren disease (n = 5 [22%]), systemic sclerosis (n = 3 [13%]), rheumatoid arthritis (n = 1 [4%]), and from ANA-positive to undifferentiated connective tissue disease (n = 3 [13%]). Fever (RR 0.89, 95% confidence interval [CI] 0.8–0.93) and antiphospholipid antibodies (RR 0.89, 95% CI 0.87–0.93) occurred less frequently, whereas arthritis (RR 1.74, 95% CI 1.20–2.55) occurred more frequently in progressors. Progressors to SLE had arthritis (91%), whereas none developed delirium, psychosis, or nephritis. Among patients with SLE, 100% fulfilled the EULAR/American College of Rheumatology (ACR) SLE criteria (sensitivity 91.7%, specificity 100%), whereas 73% fulfilled the 1997 ACR SLE criteria (sensitivity 81.8%, specificity 98.9%).

Conclusion. Most undifferentiated/asymptomatic individuals with ANA do not progress to a SARD over a two-year period. SLE progressors appear to have mild disease in the short term. The EULAR/ACR SLE criteria have improved ability to identify those who develop SLE.

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SIGNIFICANCE & INNOVATIONS

- Most undifferentiated and asymptomatic patients with antinuclear antibodies (ANAs) do not progress to a systemic autoimmune rheumatic disease (SARD) in the short term.
- Among progressors, systemic lupus erythematosus (SLE) is the most common SARD.
- Among ANA-positive individuals, a risk factor for progression to a SARD, and to SLE specifically, is the presence of arthritis.
- The European Alliance of Associations for Rheumatology/American College of Rheumatology (ACR) classification criteria for SLE have improved the ability to identify those who develop SLE compared to 1997 ACR classification criteria.

INTRODUCTION

The study of preclinical disease is an important area of research. Patients and clinicians want to know who will progress to a systemic autoimmune rheumatic disease (SARD). Researchers want to identify those in whom early intervention may prevent development of disease. For example, preclinical systemic lupus erythematosus (SLE) is a spectrum encompassing scenarios of autoantibodies with or without the presence of lupus-related signs or symptoms. A variety of nomenclatures have been proposed for this prediagnostic state including latent,[1] potential, incomplete, and early lupus.[2] All have been proposed to describe the disease in individuals who cannot be diagnosed with definite SLE but are at risk of developing the disease in longitudinal follow-up. We and others have demonstrated that individuals at risk for SLE have a greater number of autoantibodies versus individuals who are less likely to progress.[3,4] These individuals display a higher percentage and higher titers of more specific autoantibodies such as anti–double-stranded DNA (anti-dsDNA), anti-Sm, or other nuclear specificities.[4] Individuals with antinuclear antibodies (ANAs) who develop a SARD have increased T helper cell populations and plasmablasts.[5,6] Immunoregulation appears to prevent development of rheumatic disease in ANA-positive individuals.[6,7]

Retrospective cohort studies of individuals with undifferentiated rheumatic disease have reported that during the disease course, between 20% and 60% of individuals will develop SLE.[8] In these previous studies, the 1997 American College of Rheumatology (ACR)[9] SLE classification or 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria[10] were used as the gold standard to classify patients with SLE. In a more recent study of 133 women with undifferentiated rheumatic disease who were not classifiable as having SLE by either the 1997 ACR or 2012 SLICC classification criteria, 17% were classified as SLE when the 2019 EULAR/ACR classification criteria for SLE[11] were applied.[12] The EULAR/ACR classification criteria for SLE use a numeric additive point system consisting of clinical and immunologic weighted items.[11,13] The presence of ANA with a titer of 1:80 or more[14] and a score of 10 or more fulfill the classification of SLE.[11] Developed using expert-based consensus and data-driven methods,[14–20] these classification criteria have excellent sensitivity and specificity[21,22] among patients with SLE with established[11] and early disease, across sexes and ethnicities.[23]

The aims of this study were to evaluate the development of a SARD over two years in undifferentiated and asymptomatic individuals with ANA. We comparatively evaluated those who did and did not develop a SARD diagnosis based on physician judgment and evaluated fulfillment of classification criteria.

MATERIALS AND METHODS

Patients. ANA-positive individuals were recruited from the Early Autoimmune Rheumatic Disease Clinic at Toronto Western Hospital, where they had been referred for evaluation of a positive ANA test. Patients were assessed at baseline and annually using a standardized form for the development of clinical signs or symptoms of a SARD[24] and fulfillment of the 1997 ACR classification criteria for SLE,[9] 2019 EULAR/ACR classification criteria for SLE,[9,13] 2013 ACR/EULAR criteria for systemic sclerosis,[25] the revised 2016 ACR/EULAR criteria for primary Sjögren's syndrome,[26] very early diagnosis of systemic sclerosis criteria,[27] or undifferentiated connective tissue disease (UCTD) (ANA-positive with one or more symptoms but not fulfilling a physician-based diagnosis or classification criteria) by board-certified rheumatologists.

Autoantibodies. ANAs were quantified by indirect immunofluorescence using the Kallestad HEp-2 kit (Bio-Rad), through the University Health Network laboratory. The serum levels of anti-dsDNA, anti-chromatin, anti-Ro, anti-La, anti-Sm, anti-SmRNP, anti-RNP, anti–Jo-1, anti–Scl-70, anti-centromere, and anti-ribosomal P antibodies were quantified using the Bioplex 2200 ANA Screening System (Bio-Rad), with the company's thresholds being used to define a positive test. Anti-Ro60 and anti-Ro52 antibodies were measured using an autoantigen microarray, as previously reported.[3]

Data collection. Data were collected from the electronic medical record and the medical charts by two data abstractors using a standardized data collection form. Data included age, sex, self-reported ethnicity using fixed categories, disease manifestations, and serology. Deidentified data were entered into a computerized database. The study was approved by Research Ethics, and all participants provided signed informed consent.

Analysis. Descriptive statistics were used to summarize the data. Risk ratios (RRs) with 95% confidence intervals (CIs) were used to evaluate the predictive validity of manifestations at baseline for progression to a SARD and progression over two years to SLE diagnosis based on physician diagnosis. Analysis was conducted using RStudio software. The primary outcome was a

physician-based diagnosis of a SARD. We also assessed fulfillment of classification criteria for different rheumatic diseases.

RESULTS

Patients. We evaluated 207 patients, of whom 14 (6.8%) were male and 193 (93.2%) were female, with a mean ± SD age of 42.6 ± 13.9 years at presentation. Self-reported ethnicity was 136 (65.7%) White, 18 (8.7%) Black, 24 (11.6%) South Asian, 20 (9.7%) East Asian, 6 (2.9%) Hispanic, and 3 (1.4%) another ethnicity not specified.

Longitudinal follow-up at two years. Of the 207 asymptomatic ANA-positive or undifferentiated patients, 23 (11%) progressed, whereas 184 (89%) did not progress. Progressors developed SLE (n = 11; 11 of 23 [48%] of progressors, 11 of 207 [6%] total cohort), Sjögren disease (n = 5; 5 of 23 [22%] of progressors, 5 of 207 [2%] total cohort), systemic sclerosis (n = 3; 3 of 23 [13%] of progressors, 3 of 207 [1%] of total cohort), rheumatoid arthritis (n = 1; 1 of 23 [4%] of progressors, 1 of 207 [0.5%] of total cohort), and from ANA-positive to UCTD (n = 3; 3 of 23 [13%] of progressors, 3 of 207 [1%] of total cohort), all based on physician diagnosis. There was no significant difference in median age of presentation between progressors (age 42 years, range 18–77 years) and nonprogressors (age 41 years, range 17–79 years).

Classification of rheumatic disease. Among patients with SLE diagnosed based on physician judgment (n = 11), 100% fulfilled the EULAR/ACR SLE classification criteria (sensitivity 91.7%, specificity 100%), whereas only 73% fulfilled the 1997 ACR SLE criteria (sensitivity 81.8%, specificity 98.9%). The one patient with rheumatoid arthritis fulfilled the 2010 ACR/EULAR rheumatoid arthritis classification criteria, two of three (66.6%) systemic sclerosis patients fulfilled the 2013 ACR/EULAR systemic sclerosis classification criteria, one of three (33.3%) systemic sclerosis patients fulfilled the very early diagnosis of systemic sclerosis criteria, and five of five (100%) patients diagnosed with Sjögren disease fulfilled the 2016 ACR/EULAR Sjögren classification criteria.

Risk of progression to a SARD diagnosis based on physician judgment. Significantly more patients of South Asian ethnicity progressed to a SARD (9.2% nonprogressors vs 30% progressors; $P = 0.003$) (Table 1). Fever (RR 0.89, 95% CI 0.85–0.93) and antiphospholipid antibodies (anti-cardiolipin or anti-β2GP1 or lupus anticoagulant) (RR 0.89, 95% CI 0.87–0.93) occurred less frequently in those who progressed to a SARD, whereas arthritis (RR 1.74, 95% CI 1.20–2.55) occurred more frequently in progressors (Table 2). Progressors to SLE had arthritis (91%), hypocomplementemia (45%), alopecia (36%), oral ulcers (27%), acute cutaneous lupus (18%), subacute cutaneous lupus (18%), and pericarditis (18%), whereas none developed delirium, psychosis, or lupus nephritis (Table 3). Fever (RR 0.95, 95% CI 0.92–0.98) and centromere antibodies (RR 0.94, 95% CI 0.91–0.98) occurred less frequently in those who progressed to SLE, whereas arthritis (RR 1.62, 95% CI 1.17–2.23) occurred more frequently in those who progressed to SLE. Evaluation of risk factors for progression to systemic sclerosis, Sjögren disease, and rheumatoid arthritis was limited by the small numbers of patients who developed these SARDs.

Table 1. Comparison of baseline characteristics

Characteristics (N = 207)	Nonprogressors (n = 184)	Progressors (n = 23)
Median age (range), y	41.0(17–79)	42(18–77)
Female sex, n (%)	171(92.9)	22(95.6)
Ethnicity, n (%)		
Hispanic	5 (2.7)	1 (4.3)
White	123 (66.8)	13 (56.5)
Black	18 (9.8)	0 (0)
South Asian	17 (9.2)	7 (30)
East Asian	18 (9.8)	2 (8.7)

DISCUSSION

This study provides interesting insights into the progression of disease over two years in undifferentiated and asymptomatic patients with ANAs. First, we found that most undifferentiated and asymptomatic patients with ANAs do not progress to a SARD in the short term. Second, we found that progression occurred more frequently among those with South Asian ethnicity and that among progressors, SLE is the most common SARD. Among ANA-positive individuals, a risk factor for progression to a SARD, and to SLE specifically, is the presence of arthritis. Third, we demonstrate that the EULAR/ACR classification criteria for SLE have improved ability to identify those who develop SLE compared to 1997 ACR classification criteria. Finally, we found that those who progress to SLE do not have severe disease in the short term. These findings have important research and pragmatic clinical implications.

We found that most undifferentiated and asymptomatic patients with autoantibodies do not progress to a SARD, specifically SLE, systemic sclerosis, Sjögren disease, or rheumatoid arthritis in the short term. This finding can be reassuring to patients. Similar in magnitude to our findings, Radin et al found that of 133 women with undifferentiated disease, 17% fulfilled the 2019 EULAR/ACR criteria in follow-up.[12] The most common baseline manifestations in our cohort were Raynaud phenomenon, arthritis, and anti-Ro antibodies. This is similar to the work of Mosca et al, in which the most common manifestation in undifferentiated patients was arthritis, which was present in up to 60% of patients.[28] Our finding of progression of 11% in the first two years is of relevance to researchers who wish to conduct observational studies and interventional trials in preclinical disease. Our point estimate can be used for sample size and power calculations in the design of these studies. This relatively low, but clinically important, estimate of progression suggests that large

Table 2. Comparison of those who progressed and did not progress to a systemic autoimmune rheumatic disease over two years*

Manifestations	Progressors (n = 23), n (%)	Nonprogressors (n = 184), n (%)	Relative risk (95% CI)
Fever	0	2 (1)	**0.89 (0.85–0.93)**
Leukopenia	3 (13)	6 (3)	1.28 (0.81–2.04)
Thrombocytopenia	2 (8.7)	1 (0.5)	1.79 (0.36–8.90)
Lymphopenia	2 (8.7)	10 (5.4)	1.05 (0.81–1.36)
Autoimmune hemolysis	2 (8.7)	0	2.69 (NA)
Nonscarring alopecia	4 (17.4)	3 (1.6)	1.81 (0.77–4.26)
Oral ulcers	2 (8.7)	2 (1)	1.49 (0.56–3.99)
Subacute cutaneous or discoid lupus	2 (8.7)	0	2.69 (NA)
Acute cutaneous lupus	2 (8.7)	3 (1.6)	1.34 (0.66–2.75)
Photosensitivity	1 (4.3)	7 (3.8)	1.00 (0.77–1.31)
Raynaud phenomenon	7 (30.4)	24 (13.0)	1.16 (0.96–1.42)
Pleural or pericardial effusion	1 (4.3)	0	1.79 (NA)
Acute pericarditis	2 (8.7)	2 (1)	1.49 (0.56–3.99)
Arthritis	12 (52.2)	13 (7.0)	**1.74 (1.20–2.55)**
Proteinuria >0.5 g per 24 h	1 (4.3)	0	1.79 (NA)
Low C3 or C4	5 (21.7)	12 (6.5)	1.25 (0.92–1.71)
Anti-dsDNA or anti-Smith	6 (26)	17 (9.2)	1.21 (0.95–1.55)
Anti-cardiolipin or anti-β2GP1 or lupus anticoagulant	0	1 (0.5)	**0.89 (0.87–0.93)**
Ro antibody	10 (43.4)	54 (29.3)	1.07 (0.96–1.21)
La antibody	5 (21.7)	14 (76.0)	1.21 (0.92–1.58)
Sm antibody	2 (8.7)	5 (2.7)	1.19 (0.74–1.91)
SmRNP antibody	3 (13.0)	11 (6.0)	1.12 (0.85–1.48)
RNP antibody	6 (26.0)	17 (9.2)	1.21 (0.95–1.55)
ScL70 antibody	1 (4.3)	11 (6.0)	0.96 (0.80–1.15)
Jo1 antibody	0	0	NA
Centromere antibody	1 (4.3)	10 (5.4)	0.97 (0.80–1.18)
Chromatin antibody	2 (8.7)	12 (6.5)	1.03 (0.83–1.28)
Ribosomal P antibody	0	0	NA

*None of the patients developed delirium, psychosis, seizures, or class II–V lupus nephritis. Bold denotes significance. CI, confidence interval; dsDNA, double-stranded DNA; NA, not applicable.

numbers of patients will be required. Interventional studies of preclinical disease risk being underpowered to detect treatment effects if they fail to take this into account.

Among those who progress to a SARD, the most common diseases were SLE, followed by Sjögren disease, systemic sclerosis, and rheumatoid arthritis. In the patients with SLE, the disease was relatively mild with cutaneous manifestations and arthritis. The severe lupus manifestations, namely lupus nephritis, neurologic manifestations, and autoimmune hemolytic anemia, did not occur in those who transitioned to SLE in the first two years. This suggests that more severe SLE manifestations evolve later in the disease course. This may be a provocative finding because investigators consider how to study preclinical and early disease and the appropriate time in the disease course for interventions to prevent severe manifestation, damage, and death.[29] Two prospective studies have suggested that there is temporal relationship between the number of years and the development of the clinical manifestation reaching the threshold of SLE.[30,31]

Few studies have comparatively evaluated characteristics of undifferentiated and asymptomatic patients with autoantibodies who do and do not progress.[32–34] We found that progressors do not have a younger age of symptom/sign onset. This contrasts with data from the RELESSER registry in which patients with undifferentiated disease were atypically older than patients with SLE when the diagnosis was first made (42.9 vs 34.6 years).[35] Similarly, Aberle et al found that 291 patients with incomplete SLE (individuals who met three ACR criteria and did not meet the 2012 SLICC criteria for SLE) were older at diagnosis than patients with SLE who fulfilled both sets of criteria (47.5 versus 42.0 years).[36]

We have identified arthritis as a risk factor for progression from preclinical disease to a SARD and to SLE. Our reporting of clinical risk factors for progression to SLE builds on work other translational science using the interferon (IFN) signature to identify those who may progress.[37] We have previously demonstrated that IFN-α and IFN-γ–driven cytokines predict progression in the following two years.[37] Interestingly, patients who transition from preclinical disease to SLE less frequently presented with fever. In established disease, noninfectious fever is frequently a manifestation of early disease.[16,38]

Together, these findings from our cohort study suggest that the undifferentiated SARD are different. Patients in this cohort presented, on average, in the fourth decade of life and did not have severe SLE at presentation or within the first two years. Fever was not a risk factor for progression and, in particular, not

Table 3. Manifestations in those who progressed and did not progress to systemic lupus erythematosus*

Manifestations	Nonprogressors (n = 196), n (%)	Progressors to SLE (n = 11), n (%)	Relative risk (95% CI)
Fever	2 (1.0)	0	**0.95 (0.92–0.98)**
Leukopenia	7 (3.6)	2 (18.2)	1.19 (0.84–1.69)
Thrombocytopenia	1 (0.5)	2 (18.2)	1.91 (0.39–9.47)
Lymphopenia	11 (5.6)	1 (9.1)	1.03 (0.86–1.22)
Autoimmune hemolysis	0	2 (18.2)	2.87 (NA)
Delirium	0	0	NA
Psychosis	0	0	NA
Seizure	0	0	NA
Nonscarring alopecia	3 (1.5)	4 (36.3)	1.93 (0.82–4.54)
Oral ulcers	2 (1.0)	2 (18.2)	1.59 (0.60–4.25)
Subacute cutaneous or discoid lupus	0	2 (18.2)	2.87 (NA)
Acute cutaneous lupus	3 (1.5)	2 (18.2)	1.43 (0.70–2.93)
Photosensitivity	7 (3.6)	1 (9.1)	1.07 (0.82–1.40)
Raynaud phenomenon	28 (14.3)	3 (27.3)	1.05 (0.93–1.19)
Pleural or pericardial effusion	0	1 (9.1)	1.90 (NA)
Acute pericarditis	2 (1.0)	2 (18.1)	1.59 (0.60–4.25)
Arthritis	15 (7.7)	10 (90.1)	**1.62 (1.17–2.23)**
Proteinuria >0.5 g per 24 h	0	1 (9.1)	1.90 (NA)
Low C3 or C4	12 (6.1)	5 (45.5)	1.34 (0.99–1.82)
Anti-dsDNA or anti-Smith	18 (9.2)	5 (45.5)	1.22 (0.98–1.52)
Anti-cardiolipin or anti-β2GP1 or lupus anticoagulant	1 (0.5)	0	0.95 (0.92–0.98)
Ro antibody	61 (31.1)	3 (27.3)	0.99 (0.93–1.06)
La antibody	17 (8.7)	2 (18.1)	1.06 (0.90–1.24)
Sm antibody	5 (2.6)	2 (18.1)	1.27 (0.80–2.04)
SmRNP antibody	11 (5.6)	3 (27.3)	1.20 (0.91–1.58)
RNP antibody	18 (9.2)	5 (45.5)	1.22 (0.98–1.52)
ScL70 antibody	11 (5.6)	1 (9.1)	1.03 (0.86–1.22)
Jo1 antibody	0	0	NA
Centromere antibody	11 (5.6)	0	**0.94 (0.91–0.98)**
Chromatin antibody	12 (6.1)	2 (18.1)	1.10 (0.89–1.37)
Ribosomal P antibody	0	0	NA

*All patients with SLE fulfilled the EULAR/American College of Rheumatology classification criteria for SLE. Bold denotes significance. CI, confidence interval; dsDNA, double-stranded DNA; NA, not applicable; SLE, systemic lupus erythematosus.

a risk factor for progression to SLE. In our study, along with the study by Mosca et al[38] related to SLE criteria development, fever was an early symptom and risk factor for progression to SLE. However, the mean age in that study was 32 years, and the patients in the current study are older by a decade. The undifferentiated patients in this study appear to be different from patients with SLE who present at a younger age, in whom fever is an early symptom, and the patients often experience more severe disease at presentation.

In our current study, we demonstrate that 2019 EULAR/ACR criteria for SLE confer added value over the 1997 ACR SLE criteria among those who transition from preclinical disease to SLE in longitudinal follow-up. Readers are cautioned that the 2019 EULAR/ACR criteria for SLE were developed for research purposes, with the goal of identifying more homogeneous groups of patients for inclusion into clinical trials, observational studies, and translational studies.[39] However, we have shown that these criteria are also useful for predicting ominous short-term (disease activity, disease flares)[40] and long-term (organ damage, death) outcomes.[41] In both classification and prognostication studies, the criteria were tested and validated in patients within an established diagnosis of SLE. In the study of preclinical disease, investigators may consider using the 2019 EULAR/ACR classification criteria for SLE as an outcome in prevention trials or prospective cohort studies of patients with undifferentiated disease. Using the 2019 EULAR/ACR criteria as an outcome shifts the paradigm and expands their utility.

Strengths of this study include the use of a standardized data collection protocol, inclusion of a diverse multiethnic cohort, and universal health care, thereby reducing the potential of access to care impacting our study findings. Potential limitations of this study are the relatively small numbers of patients who developed disease and the small number of male patients, precluding our ability to make any sex-based inferences. Our duration of follow-up is currently limited to two years, so we are unable to make inferences about progression to a SARD in the long term. An increase in sample size and longer duration of follow-up may allow for the detection of disease and allow for additional subset analyses. Finally, it may be that most individuals with nonspecific autoantibodies will not progress to a SARD in the short term and that

certain ethnic groups are disproportionately afflicted by SARDs, particularly SLE. Those with the most severe phenotypes may present earlier and, hence, not be captured in this study. This may explain why those who did progress to a SARD had milder disease.

In summary, most undifferentiated and asymptomatic patients with autoantibodies do not progress to a SARD in the short term. Researchers conducting interventional studies in preclinical disease will need to ensure these studies are adequately powered to detect treatment effects. Progressors most frequently developed SLE and the 2019 EULAR/ACR SLE classification criteria, compared to 1997 SLE classification criteria, have improved the ability to classify those who transition from preclinical disease to SLE. Progressors to SLE appear to have mild disease in the short term.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Johnson confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Helsinki Declaration requirements.

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