Burden of autoantibodies and association with disease activity and damage in systemic lupus erythematosus

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Abstract

Objective

To determine whether immunological burden of autoantibodies as reflected by the number of cumulative antibodies present at inception and after 3 and 5 years is associated with or predicts subsequent disease activity and damage in lupus.

Methods

Patients with SLE followed from inception at a single centre between 1992 and 2007 were included. Twelve autoantibodies were assayed in each patient at years 1, 3 and 5 of disease. The relationship between the burden of autoantibodies and outcomes, SDI (Systemic Lupus International Collaborative Clinics Damage Index), AMS (Adjusted Mean SLEDAI-2K) and AMS excluding anti-ds DNA (AMS-DNA) was evaluated as an association and as prediction. We determined the association between autoantibody burden and outcomes at years 1, 3 and 5 and the prediction using autoantibody burden at year 1 and year 3 to predict outcomes at years 3 and 5 respectively.

Results

Between 1992 and 2007, 235 inception patients were identified. Of these, 223, 163 and 129 patients had 10 or more autoantibodies tested at years 1, 3 and year 5 following diagnosis respectively. There was no association between the burden at years 1, 3 and 5 and outcome measures at years 1, 3 and 5 respectively. Furthermore, burden of autoantibodies at years 1 and 3 did not predict the outcome measures at years 3 and 5, respectively.

Conclusions

Immunological burden in SLE at years 1, 3 or 5 as reflected by the number of autoantibodies found, was not associated with or predictive of subsequent disease activity or damage over time.

Key words

Systemic lupus erythematosus, autoantibodies, outcomes

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, which is highly variable in patterns of organ involvement and prognosis. A number of autoantibodies in SLE patients have been useful for classification and diagnostic purposes or have been associated with specific clinical features. Antinuclear antibodies (ANA) were initially discovered in the 1940s using the lupus erythematosus (LE) cell test (1). However, the LE cell test has generally been replaced by the fluorescent antinuclear antibody test. ANAs are the most prevalent antibodies, occurring in approximately 93% of patients and high titers correlate with pathologic significance (1). ANA can also be found in association with many other autoimmune disorders and thus lacks specificity. Anti-ds DNA, anti-Sm, LE cells, and antiphospholipid antibodies (aPL) are useful for diagnostic purposes (1-11). Some antibodies are associated with specific clinical features; *e.g.* anti-ds DNA is associated with nephritis, anti-Ro antibodies are associated with cutaneous lupus, photosensitivity and neonatal lupus, anti-Ro and anti-La antibodies are associated with Sjögren's syndrome, and anticardiolipin antibodies (aCL) and lupus anticoagulant with pregnancy loss and thrombosis (4-11). Anti-Sm antibodies are detected in 10-30% of lupus patients and have high specificity for lupus. Anti-Sm antibodies have shown associations with general/constitutional symptoms, lupus nephritis and central nervous system disease (3, 4, 6). Lupus patients with anti-RNP autoantibodies tend to have myositis, Raynaud's phenomenon and overlap syndrome, and are less likely to develop lupus nephritis (4, 12). Anti-Scl-70 has been reported to have a good correlation with disease activity and suggests increased risk for pulmonary hypertension and nephritis (13).

While certain autoantibodies correlate with disease activity, it is not clear whether the immunological burden, as reflected by the number of antibodies present, is predictive of subsequent disease activity or damage. The objective of this study was to determine whether immunological burden, indicated by multiple autoantibody profiling at inception and during the first 5 years, is associated with disease activity and damage and predicts subsequent disease activity and damage in SLE.

Materials and methods

Patient selection and assessment

Patients were selected from the University of Toronto Lupus Clinic. Patients with SLE [≥4 American College of Rheumatology (ACR) criteria or 3 ACR criteria plus a typical histological lesion of SLE on renal or skin biopsy] have been followed prospectively at the University of Toronto Lupus Clinic since 1970. All inception patients seen in the clinic within 12 months of diagnosis from 1992-2007 were included. Patients attend the Lupus Clinic at 2-6 month intervals regardless of the state of activity of their lupus. The standard protocol includes: complete history, physical examination, and laboratory evaluation.

Serology

ANA was determined yearly by indirect immunofluorescence with HEp2 cells (Human epithelial cell tumour line). Detection of antinuclear antibodies at a dilution of ≥1:80 were considered positive. Anti-Ro, anti-La, anti-Sm, anti-RNP, anti-Scl-70 and anti-Jo-1 were assayed yearly by enzyme-linked immunosorbent assays (ELISA) (extractable nuclear antigens (ENA) were assayed using the ELISA test systems for the detection of IgG antibodies to Jo-1, Sm, RNP, Ro, La and Scl-70; Zeus Scientific, Raritan, NJ, USA). ANCA were determined yearly by ELISA (MPO IgG and Proteinase-3 IgG ELISA test system; Zeus Scientific, Raritan, NJ, USA) and total anticardiolipin antibodies and individual anticardiolipin antibodies (aCL IgG/aCL IgM) (Phadia Varelisa kits, Somagen for anticardiolipin antibodies screen and IgG and IgM assays) were measured yearly by ELISA. Before April 13, 2005 only anticardiolipin antibodies were determined. IgG aCL levels >13 GPL-U/ml and IgM a CL levels >13 MPL-U/ml were considered positive. The clotting assays for lupus anticoagulant included the dilute Russell viper venom time (dRVVT) and the platelet neutralisation procedure (PNP); however, this has been

done only over the last 4 years. LE cells were reported as seen or none seen and Coombs' test as positive or negative. Anti-ds DNA antibodies were assayed using the Farr (Amerlex anti-ds DNA radioimmunoassay kit; Trinity Biotech, Bray, Ireland) and ELISA (ds DNA ELISA test system; Zeus Scientific, Raritan, NJ, USA), which are components of the usual clinic protocol. The Farr assay was used to determine the presence and levels of anti-ds DNA at each visit, as it correlates better with disease activity (14). Patients with a minimum of 10 autoantibodies tested were included. The number of positive antibodies was determined in each patient at the first year and repeated in the same patients at 3 and 5 years.

Predictor variables

The number of positive autoantibodies, the immunological burden, was the predictor variable. This was determined at years 1 and 3 to predict outcomes at years 3 and 5.

Outcome variables

Disease activity is measured by the Systemic Lupus Erythematosus Disease activity Index 2000 (SLEDAI-2K), a vaAid measure of disease activity in SLE. This is a validated modification of the SLEDAI, an instrument validated to assess disease activity in SLE, which has been shown to be reliable, sensitive to change, and easily performed by both experts and non-experts (15-18). All items necessary to complete the SLEDAI-2K are included in the protocol.

The adjusted mean SLEDAI-2K (AMS) was constructed within each defined calendar period for each patient from a patient's SLEDAI-2K measurements within the calendar period and is a measure of "area under the curve" of SLEDAI-2K divided by time (19). AMS has the same units as the original SLEDAI-2K. Because anti-ds DNA occurs commonly and impacts SLEDAI-2K and AMS scores, we repeated the analysis excluding anti-ds DNA (AMS-DNA). Both AMS and AMS-DNA were determined at years 1, 3 and 5 for all lupus patients in the study.

Organ damage is assessed using the SLICC/ACR Damage Index (SDI) (20). This instrument records damage in 12 systems reflecting non-reversible accumulated damage since the onset of SLE, without attribution. This instrument has been shown to be valid and reproducible (20, 21). All items have been recorded prospectively in the database. The SDI is completed once yearly.

The outcome variables were determined as follows: SDI, AMS and AMS-DNA at years 1, 3 and 5.

Statistical analysis

Demographic features of the study group were evaluated using descriptive statistics. The number of positive autoantibodies present for each patient was calculated and constitutes the burden at years 1, 3 and 5. The accrual over the 5 years from inception is plotted for each of the 12 autoantibodies.

The relationship between autoantibody burden and outcomes was evaluated as an association and as prediction. We looked at association between autoantibody burden and outcomes at years 1, 3 and 5 and at prediction using autoantibody burden at years 1 (to predict outcomes at years 3 and 5) and burden at year 3 (to predict outcomes at year 5). In all cases, the relationship was evaluated through correlation coefficients and linear regression.

We further categorised the total number of positive autoantibodies as ≤4 or >4. Using this categorisation, we applied *t*-tests to compare the association and prediction as outlined above.

Table I. Characteristics of the systemic lupus erythematosus cohort*.

Age	36.4 ± 13.3	
Age at diagnosis	36.2 ± 13.0	
Sex	Female 85%	
Race	Caucasian 61%	Black 13%
	Asian 11%	Other 15%
Length of follow up in clinic (from 1st to last clinic visit) (years)	6.7 ± 4.1	
SLE duration at first clinic visit (years)	0.2 ± 0.3	
SLEDAI-2K at 1st clinic visit	10.1 ± 7.6	
Use of steroids ever within 1 year from diagnosis	70%	
Use of immunosuppressive ever within 1year from diagnosis	35%	
Use of antimalarial ever within 1 year from diagnosis	67%	

*Values are the number (percentage) unless otherwise indicated; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; AMS: adjusted mean SLEDAI; CAD: Coronary artery disease; AVN: Avascular necrosis.

Results

Patients' demographics

Between 1992-2007, a total of 235 inception patients were identified with a mean age of 36.4±13.3 years. The majority of the 235 patients were female (85%). The patients' ethnic distribution was: Caucasian 61%, Black 13%, Asian 11%, and other 15%. The mean and standard deviation of the length of follow up in clinic from the first visit to last clinic visit was 6.7±4.1 years. The duration of SLE at first clinic visit was 0.2±0.3 years. The disease activity at first clinic visit by SLEDAI-2K was 10.1±7.6. The use of steroids, immunosuppressive and antimalarial drugs ever within 1 year from diagnosis was found to be 70%, 35% and 67% of the patients, respectively (Table I).

Patient autoantibody make up

In terms of serologic tests, 223, 163 and 129 patients had 10 or more autoantibodies assayed at years 1, 3 and 5 respectively. By analysing the data of 120 patients that had 10 or more autoantibodies assayed at years 1, 3 and 5, we further determined the patient's mean number of positive autoantibodies and their make up. The mean number of positive autoantibodies was 4.75±2.32, 5.37±2.48 and 5.79±2.51 at years 1, 3 and 5 respectively. At year 1, 98% of the patients had a positive ANA and by year 5 the percentage of patients with positive ANA rose to 99%. The second most frequently encountered antibody was anti-ds DNA; 68%, 73% and 78% at years 1, 3 and 5 respectively. The accrual of autoantibodies by year 3 and 5 for anti-Ro was minor; 2% and 1% respectively, and the accrual of autoantibodies to Jo-1 by year 3 and 5 was 4% and 2% respectively. The accrual of

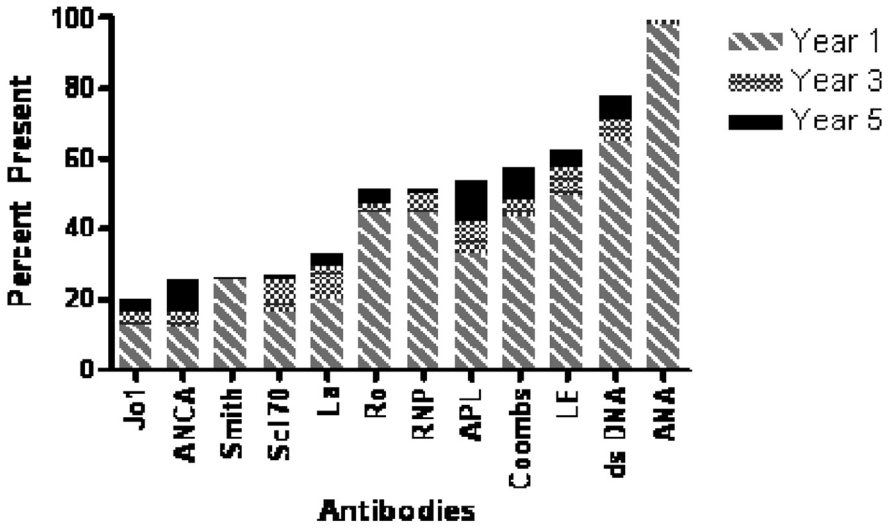

Fig. 1. The plot of the autoantibody accrual over 5 years.

Table II. Make up of autoantibody burden in 120 patients for year 1, 3 and 5* in 120 patients.

	Year 1 (n=120)	Year 3 (n=120)	Year 5 (n=120)
Anti-ds DNA	68%	73%	78%
Anti-Smith	22%	23%	27%
Anti-Ro (SSA)	45%	47%	48%
Anti-La (SSB)	26%	30%	30%
Anti-RNP	42%	50%	51%
Anti-Scl-70	20%	23%	26%
Anti-Jo-1	14%	18%	20%
ANCA	9%	17%	25%
Coombs' test	44%	55%	61%
LE cells	53%	60%	62%
ANA	98%	98%	99%
aPL	38%	43%	53%
Mean number of antibodies	4.75 ± 2.32	5.37 ± 2.48	5.79 ± 2.51

*Values are percentage and number unless otherwise indicated. aPL: anti-phospholipid antibodies.

anti-La, anti-RNP, anti-Scl-70, ANCA, LE cells, and anti-phospholipid antibodies by year 3 in comparison to year 1 was sometimes more evident; 4%, 8%, 3%, 8%, 7% and 5% respectively, and by year 5 in comparison to year 1 was 4%, 9%, 6%, 16%, 9% and 15% respectively (Fig. 1 and Table II). The mean number of positive autoantibodies and their make up did not differ significantly in each of the 223, 163 and 129 patients at years 1, 3 and 5, respectively (data not provided).

Association between autoantibody burden at years 1, 3 and 5 and outcomes (SDI, AMS and AMS-DNA)
– SDI.
The SDI was 0.47±0.96 at year 1, 0.74±1.19 at year 3 and 0.95±1.27 at year 5. No association could be determined between burden at year 1 and SDI year 1 (p=0.56), burden at year 3 and SDI year 3 (p=0.30) and burden at year 5 and SDI year 5 (p=0.82) (Table III). Using the categorisation of positive autoantibodies as ≤4 or >4 we could not show an association between burden at year 1 and SDI year 1 (p=0.93) and burden at year 3 and SDI year 3 (p=0.64) (Table IV).

– AMS
The AMS was 6.74±4.59 at year 1, 5.49±3.66 at year 3 and 5.04±3.21 at year 5. There was a statistically significantly association between burden at year 1 and AMS year 1 (p=0.002), burden at year 3 and AMS year 3 (p=0.004) and burden at year 5 and AMS year 5 (p=0.007) (Table III). Using the categorisation of positive autoantibodies as ≤4 or >4 we showed a statistically significantly association between burden at year 1 and AMS year 1 (p=0.015) and burden at year 3 and AMS year 3 (p=0.04) (Table IV).

– AMS-DNA
The AMS-DNA was 5.79±4.34 at year 1, 4.63±3.38 at year 3 and 4.26±2.93 at year 5. No significant association could be determined between burden at year 1 and AMS-DNA year 1 (p=0.07), burden at year 3 and AMS-DNA year 3 (p=0.10) and burden at year 5 and AMS-DNA year 5 (p=0.14) (Table III). Using the categorisation of positive autoantibodies as ≤4 or >4 we could not show an association between burden at year 1 and AMS-DNA year 1 (p=0.18) and burden at year 3 and AMS-DNA year 3 (p=0.29) (Table IV).

Prediction of outcomes (SDI, AMS and AMS-DNA) using autoantibody burden at years 1 (to predict outcomes at years 3 and 5) and burden at year 3 (to predict outcomes at year 5).
– SDI
The burden at year 1 did not predict SDI year 3 (0.76±1.20; p=0.48) and year 5 (0.97±1.29; p=0.18). The burden at year 3 did not predict SDI year 5 (0.94±1.27; p=0.49) (Table IIIa). Using the categorisation of positive autoantibodies as ≤4 or >4 the burden of autoantibodies at year 1 did not predict SDI year 3 (p=0.53) and SDI year 5 (p=0.38). The burden at year 3 did not predict SDI year 5 (p=0.20) (Table IVa).

– AMS
The burden at year 1 predicted AMS at year 3 (5.54±3.71; p=0.005) and year 5 (5.12±3.25; p=0.02). The burden at year 3 did predict AMS at year 5 (5.05±3.22; p=0.007) (Table IIIa). Using the categorisation of positive autoantibodies as ≤4 or >4 the burden of autoantibodies by year 1 predicted AMS year 3 (p=0.018) and AMS year 5 (p=0.03). The burden by year 3 did not predict AMS year 5 (p=0.14) (Table IVa).

– AMS-DNA
The burden at year 1 did not predict

Table III. Association between autoantibody burden by year 1, 3 and 5 and SDI, AMS and AMS-DNA*.

	Mean ± Std	Regression parameter estimate ± SE	Correlation Coefficient	*p*-value
		Burden of autoantibodies at Year 1		
SDI Year 1	0.47 ± 0.96	0.02 ± 0.03	0.04	0.56
AMS Year 1	6.74 ± 4.59	0.42 ± 0.13	0.21	0.002
AMS-DNA Year 1	5.79 ± 4.34	0.23 ± 0.12	0.12	0.07
		Burden of autoantibodies at Year 3		
SDI Year 3	0.74 ± 1.19	0.04 ± 0.04	0.08	0.30
AMS Year 3	5.49 ± 3.66	0.33 ± 0.11	0.23	0.004
AMS - DNA Year 3	4.63 ± 3.38	0.17 ± 0.11	0.13	0.10
		Burden of autoantibodies at Year 5		
SDI Year 5	0.95 ± 1.27	-0.01 ± 0.005	-0.02	0.82
AMS Year 5	5.04 ± 3.21	0.31 ± 0.11	0.24	0.007
AMS-DNA Year 5	4.26 ± 2.93	0.15 ± 0.10	0.13	0.14

*Values are numerical.
SDI: Systemic Lupus International Collaborative Clinics Damage Index; AMS: Adjusted Mean SLEDAI-2K; AMS-DNA: Adjusted Mean SLEDAI-2K excluding DNA.

Table IIIa. Prediction at years 3 and 5: autoantibody burden by year 1 and 3 and SDI, AMS and AMS-DNA*.

	Mean ± Std	Regression parameter estimate ± SE	Correlation Coefficient	*p*-value
		Burden of autoantibodies at Year 1		
SDI Year 3	0.76 ± 1.20	0.03 ± 0.04	0.06	0.48
AMS Year 3	5.54 ± 3.71	0.35 ± 0.12	0.23	0.005
AMS-DNA Year 3	4.69 ± 3.43	0.18 ± 0.12	0.13	0.11
		Burden of autoantibodies at Year 1		
SDI Year 5	0.97 ± 1.29	-0.07 ± 0.05	-0.12	0.18
AMS Year 5	5.12 ± 3.25	0.30 ± 0.13	0.22	0.02
AMS-DNA Year 5	4.35 ± 2.99	0.15 ± 0.12	0.12	0.21
		Burden of autoantibodies at Year 3		
SDI Year 5	0.94 ± 1.27	-0.03 ± 0.05	-0.06	0.49
AMS Year 5	5.05 ± 3.22	0.31 ± 0.11	0.24	0.007
AMS-DNA Year 5	4.27 ± 2.94	0.16 ± 0.11	0.13	0.13

*Values are numerical.
SDI: Systemic Lupus International Collaborative Clinics Damage Index; AMS: Adjusted Mean SLEDAI-2K; AMS-DNA: Adjusted Mean SLEDAI-2K excluding DNA.

AMS-DNA year 3 (4.69±3.43; p=0.11) and year 5 (4.35±2.99; p=0.21). The burden at year 3 did not predict AMS-DNA year 5 (4.27±2.94; p=0.13) (Table IIIa). Using the categorisation of positive autoantibodies as ≤4 or >4 the autoantibody burden at year 1 did not predict AMS-DNA year 3 (p=0.16) and AMS-DNA year 5 (p=0.14). The burden at year 3 did not predict AMS-DNA year 5 (p=0.52) (Table IVa).

Discussion

Autoantibody production is the hallmark of lupus disease. Patients with SLE have already accrued a significant number of autoantibodies prior to the diagnosis indicating a polyclonal activation preceding the clinical presentation of SLE. In general, the rate of appearance of antibodies continues to increase until the time of diagnosis of SLE (8, 22). However, the clinical implication of this burden of antibodies on the disease outcome over time is unknown.

We have shown in this study that patients continued to accrue all types of autoantibodies by years 3 and 5. Nevertheless, the rate of autoantibody accrual after diagnosis was small. Whether the number of autoantibodies will continue to increase or plateau after 5 years is yet to be determined. This minimal accrual of autoantibodies suggests that either the polyclonal activation of the immune system has reduced after developing clinical lupus or that it is being suppressed by the medications. In fact, the majority of our patients received antimalarials, prednisone and/or immunosuppressive agents within 1 year from diagnosis.

A significant portion of the autoantibody load of a patient with SLE is present at diagnosis. Thus one might have predicted that antibody accrual within the first and third years might predict burden of future disease. Based on this hypothesis, we examined the burden of future disease by studying disease activity over time and damage accrual over time in relation to autoantibody production. This study represents a large cohort, and is one of the first to longitudinally assess whether the burden of autoantibodies at inception is a useful predictor of later disease activity and damage in SLE.

Our study shows that at years 1, 3 and 5 the burden of autoantibodies was not associated with damage index (SDI) and the association with disease activity (AMS) was lost when anti-ds DNA was removed from the calculation of AMS. Indeed, anti-ds DNA occurred commonly; 65%-78% by year 1 and 5 respectively, and impacted on SLEDAI-2K and AMS scores. Thus it is more a specific antibody (anti-ds DNA) rather than antibody burden that is associated with disease activity.

Moreover, the burden of autoantibodies at year 1 did not predict the damage index at years 3 and 5 and the statistically significant prediction for disease activity was lost when anti-ds DNA was removed from the calculation of AMS. Similarly the burden of autoantibodies at year 3 did not predict the damage index at year 5 nor did cumulative disease activity (AMS) after excluding anti-ds DNA from AMS. Thus again it is more the specific antibody (anti-ds DNA) rather than antibody burden that predicted disease activity

Our study demonstrates that immunological burden in SLE at years 1, 3 or 5 as reflected by the number of autoantibodies found, was not associated with nor predictive of subsequent disease

Table IV. Association between autoantibody burden by year 1, 3 and SDI, AMS, AMS-DNA by categorisation of the number of positive autoantibodies as ≤4 or >4*.

	Burden of autoantibodies at Year 1 Mean ± Std		
	≤4 positive autoantibodies at year 1 (n=129)	>4 positive autoantibodies at year 1 (n=106)	*p*-value
SDI Year 1	0.46 ± 0.08	0.47 ± 0.09	0.93
AMS Year 1	5.94 ± 0.35	7.43 ± 0.49	0.015
AMS-DNA Year 1	5.30 ± 0.33	6.08 ± 0.47	0.18
	Burden of autoantibodies at Year 3		
	≤4 positive autoantibodies at year 3 (n=70)	>4 positive autoantibodies at year 3 (n=96)	*p*-value
SDI Year 3	0.69 ± 0.13	0.78 ± 0.13	0.64
AMS Year 3	4.77 ± 0.42	5.97 ± 0.38	0.04
AMS-DNA Year 3	4.28 ± 0.38	4.84 ± 0.36	0.29

*Values are numerical.
SDI: Systemic Lupus International Collaborative Clinics Damage Index; AMS: Adjusted Mean SLEDAI-2K; AMS-DNA: Adjusted Mean SLEDAI-2K excluding DNA.

Table IVa. Prediction of SDI, AMS, AMS-DNA at year 3 and 5: by categorisation of the number of positive autoantibodies as ≤4 or >4 by year 1 and 3 respectively*.

	Mean ± Std	Mean ± Std	*p*-value
	Burden of autoantibodies at Year 1		
	≤4 positive autoantibodies at year 1 (n=129)	>4 positive autoantibodies at year 1 (n=106)	
SDI Year 3	0.69 ± 0.11	0.81 ± 0.15	0.53
AMS Year 3	4.83 ± 0.36	6.18 ± 0.44	0.018
AMS-DNA Year 3	4.26 ± 0.32	4.99 ± 0.42	0.16
	Burden of autoantibodies at Year 1		
	≤4 positive autoantibodies at year 1 (n=129)	>4 positive autoantibodies at year 1 (n=106)	
SDI Year 5	1.07 ± 0.17	0.87 ± 0.15	0.38
AMS Year 5	4.45 ± 0.36	5.68 ± 0.42	0.03
AMS-DNA Year 5	3.89 ± 0.33	4.65 ± 0.39	0.14
	Burden of autoantibodies at Year 3		
	≤4 positive autoantibodies at year 3 (n=70)	>4 positive autoantibodies at year 3 (n=96)	
SDI Year 5	1.15 ± 0.19	0.86 ± 0.14	0.20
AMS Year 5	4.55 ± 0.42	5.39 ± 0.37	0.14
AMS-DNA Year 5	4.06 ± 0.39	4.39 ± 0.33	0.52

*Values are numerical.
SDI: Systemic Lupus International Collaborative Clinics Damage Index; AMS: Adjusted Mean SLEDAI-2K; AMS-DNA: Adjusted Mean SLEDAI-2K excluding DNA.

activity or damage over time. Whether particular autoantibody clusters will impact the disease manifestations and/or outcomes in lupus patients remains to be determined.

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