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Risk and protective factors for thrombosis in systemic lupus erythematosus:

results from a large, multi-ethnic cohort

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Abstract

Objectives—Few studies have examined thrombosis in systemic lupus erythematosus (SLE), none have included Asian-Americans, and most have had small sample sizes. We analysed risk factors for thrombosis in a large, multiethnic SLE cohort.

Methods—We studied 1930 SLE subjects, including Caucasians, African-Americans, Asian-Americans and Hispanics. Data were derived from questionnaires and medical records. Documented history of thrombosis was the primary outcome. Explanatory variables included age at SLE diagnosis, gender, ethnicity, disease duration, smoking, antiphospholipid antibody (aPL) status, nephritis and specific medications.

Results—Smoking (OR 1.26, $p = 0.011$), longer disease duration (OR 1.26 per 5 years $p = 0.027 \times 10^{-7}$), nephritis (OR 1.35, $p = 0.036$), aPL positivity (OR 3.22, $p < 10^{-9}$) and immunomodulating medication use (OR 1.40, $p = 0.011$) were statistically significant risk factors for thrombosis. Younger age at SLE onset was protective (OR 0.52 for age ≤ 20 , $p = 0.001$). After adjusting for disease severity and incorporating propensity scores, hydroxychloroquine use remained significantly protective for thrombosis (OR 0.62, $p = 4.91 \times 10^{-4}$).

Conclusions—This study confirms that older age at onset, longer disease duration, smoking, aPL positivity, history of nephritis and immunomodulating medication use are risk factors for thrombosis in SLE. These data are the first to confirm in a large and ethnically diverse SLE cohort that hydroxychloroquine use is protective for thrombosis.

Thrombosis causes substantial morbidity and mortality in systemic lupus erythematosus (SLE) and occurs with greater frequency and at a younger age than in the general population.¹ Although several risk factors for thrombosis in SLE have been identified,² these do not completely explain the thrombosis burden. Antiphospholipid antibody (aPL) positivity has been one of the most frequently studied risk factors for thrombosis in SLE.^{3–5} These autoantibodies have been associated with an increased risk of venous and arterial thrombosis but the mechanism by which these antibodies increase risk is not well understood.³ Interestingly, in the general population, ethnicity also appears to influence thrombosis risk.² Such ethnic differences have not been well-studied in SLE, although patients with SLE of certain ethnic subgroups experience worse outcomes.⁶

Our goal was to identify risk factors for thrombosis in SLE using a large and ethnically diverse study sample that has also been characterised for a wide range of potential risk factors.

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PATIENTS AND METHODS

We studied 1930 patients from the UCSF Lupus Genetics Project, a multiethnic cohort of patients with SLE.⁷ The protocol was approved by the Institutional Review Board at the University of California, San Francisco (California, USA). Subjects were recruited from hospitals, community rheumatology clinics, lupus support groups, referral centres in northern California, and nationwide outreach efforts. SLE diagnosis was rigorously confirmed by medical record review according to the American College of Rheumatology (ACR) criteria.⁸ Baseline questionnaire data included demographic information, clinical characteristics and behavioural factors.

Covariates examined as potential predictor variables included ethnicity, smoking, age at SLE diagnosis, duration of SLE and immunomodulating medications (see table 1 for specific medications examined and other variable definitions). Medication history was collected by questionnaire, supplemented by medical record information and analysed as “ever” versus “never use”.

Medical records obtained from patients’ rheumatologists or other treating physicians were reviewed to document thromboses reported in patient questionnaires and identify any additional thromboses. Thrombosis events included deep vein thrombosis, pulmonary embolism, cerebral vascular accident, myocardial infarction, retinal vein thrombosis and miscarriage (three consecutive events in the first trimester or ≥ 1 in the second or third trimesters). Medical records were also reviewed for results of aPL testing, including lupus anticoagulant (LAC) measured by Russell Viper Venom Time (RVVT) and anticardiolipin (ACL) IgG or IgM autoantibodies. Subjects were considered aPL positive if at least one of these autoantibodies were documented.

Explanatory variables potentially influencing thrombosis risk were examined for association in bivariate analysis using the χ^2 test (for categorical variables) and Student’s t-test (for continuous variables). These variables included aPL status, ethnicity, smoking, duration of disease, age at SLE diagnosis, medication use history and history of nephritis. In multivariate analyses, we used logistic regression to analyse associations between significant predictor variables identified from the preliminary bivariate analyses and risk of thrombosis. Odds ratios and 95% confidence intervals were calculated.

Subgroup analyses were then performed in which the explanatory variable aPL was considered separately as LAC and ACL (IgG or IgM) and immunomodulating medications were considered individually. Sensitivity analyses were performed to analyse venous and arterial thromboses separately. We also performed subgroup analyses to compare results when socio-economic status indicators (education and income) were included as covariates.

To further evaluate the protective effect of hydroxychloroquine and thrombosis risk observed in the current study, we used propensity scores to adjust for confounding by indication.^{10 11} All statistical analyses were performed using the STATA SE software, version 9.0 (StataCorp, College Station, Texas, USA).

RESULTS

Characteristics for the 1930 SLE study participants are shown in table 1. Four hundred and twenty-six subjects (22%) had at least one documented thrombosis, 119 (6%) subjects had two or more documented thromboses, and 516 subjects (27%) were aPL positive.

Explanatory variables associated with thrombosis in bivariate analyses are shown in table 2.

Explanatory variables found to increase the risk for thrombosis in the multivariate model (table 3) included smoking (OR 1.26, $p = 0.011$), nephritis (OR 1.35, $p = 0.036$), aPL positivity (OR 3.22, $p < 10^{-9}$), disease duration (OR 1.26 per 5 years with SLE, $p = 0.027 \times 10^{-7}$) and immunomodulating medications (OR 1.40, $p = 0.011$). We found that younger age at SLE diagnosis was protective for thrombosis in our multivariate model (OR 0.52, $p = 0.001$ for age ≤ 20 years at diagnosis). Treatment with hydroxychloroquine was protective for thrombosis when adjusting for other explanatory variables (OR 0.67, $p = 0.008$). When the propensity scores were added as a covariate to the original model using logistic regression, the association between hydroxychloroquine use and thrombosis remained significantly protective (OR 0.62, $p = 4.91 \times 10^{-4}$).

Results of subgroup analyses indicated that history of treatment with azathioprine (OR 1.36, $p = 0.023$) and cyclophosphamide (OR 1.42, $p = 0.025$) were significant risk factors for thrombosis as was ACL positivity (OR 2.02, $p = 0.037 \times 10^{-4}$). Analysis of a subgroup of 222 patients with ACL titres available indicated that a high ACL titre was more strongly associated with thrombosis than low or intermediate titre (OR 2.08, $p = 0.058$). Further, results of sensitivity analyses indicated that African-American ethnicity showed a protective trend for venous thromboses (OR 0.49, $p = 0.066$), Asian-American ethnicity was specifically protective for deep vein thrombosis (OR 0.41, $p = 0.047$), and female gender was protective for pulmonary embolism (OR 0.40, $p = 0.022$) and myocardial infarction (OR 0.49, $p = 0.049$). Finally, when subjects with multiple thromboses were compared with subjects who had no thrombosis, results were similar but with more pronounced ORs (table 3).

DISCUSSION

These findings confirm in a large, multi-ethnic SLE cohort that patients with aPL positivity, a history of smoking, immunomodulating medication use, longer disease duration and older age at SLE onset are more likely to have had at least one thrombosis. Importantly, these data are the first to confirm in a large and ethnically diverse study sample that hydroxychloroquine use is protective. Furthermore, these data suggest that Asian-American and African-American ethnicity as well as female gender may be protective for certain thrombosis subtypes, though these findings require confirmation in other study populations.

aPL positivity is a well-established risk factor for thrombosis. Love and Santoro found that 42% of LAC positive and 40% of patients with SLE who were ACL positive had a history of thrombosis.¹² We found that, when controlling for other explanatory variables, subjects who were aPL positive had more than three times the odds of having an event compared with aPL-negative subjects, confirming previous research findings.

The first study to show that smoking was a significant risk factor for vascular events in SLE was by Toloza *et al.*⁴ Other studies that focused on cardiovascular thrombosis events in SLE demonstrated that older age at diagnosis and longer duration of disease also increase risk for thrombosis.^{4 13} Our study reinforces these findings.

That thrombosis risk may differ for African-American and Asian-American patients with SLE is a new finding. Because this study controlled for important risk factors and potential sources of confounding, it appears that Asian-Americans and African-American patients with SLE may have different, yet unidentified, risk factors for thrombosis compared with other ethnic groups. Explanations offered in previous investigations include the lower prevalence of known genetic risk factors (eg, factor V Leiden polymorphism) for ethnic groups other than Caucasians and the lower prevalence of obesity in Asian-Americans.² Other risk factors that might differ between ethnic groups, such as smoking and disease severity, were controlled for in our study and, therefore, are unlikely to explain these differences in thrombosis rates. In addition, results

of an analysis performed for a subgroup of 800 patients for which levels of income and education were accounted for were consistent with our main results (data not shown). However, potential false positive findings resulting from multiple testing and the smaller sample sizes in our sensitivity analyses necessitate confirmation of these results.

Our finding that hydroxychloroquine use is protective for thrombosis is intriguing. Hydroxychloroquine use has been suggested to offer protection from thrombosis in a few small previous studies.¹⁴⁻¹⁶ Hydroxychloroquine has antithrombotic potential through multiple mechanisms, including inhibition of platelet aggregation and adhesion,¹⁷ cholesterol-lowering mechanisms¹⁷ and blockade of aPL production.¹⁸

Limitations of our study relate primarily to its retrospective nature. Because patients were recruited from a variety of settings, aPL were measured in different labs using a variety of assays. In addition, aPL were measured in the context of clinical care and not necessarily at the time of thrombosis. As a result, these autoantibodies may have been checked more frequently in patients who experienced a thrombosis (resulting in ascertainment bias). Although we did not have standardised measures of SLE severity or damage, we did have extensive information about disease severity that allowed us to account for this important factor in our analyses. We found that immunomodulating medications and hydroxychloroquine use were significantly associated with (or protective for) thrombosis risk. Further, our use of propensity scores supports a protective effect of hydroxychloroquine treatment as opposed to an association with mild disease.

In summary, this study confirms that certain risk factors suggested in previous, smaller, studies are significantly associated with thrombosis in patients with SLE and identifies additional risk factors that may influence this important SLE outcome. Additional work is needed to clarify ethnic differences in thrombosis in SLE, particularly explanatory variables for these differences. Importantly, this study also provides rigorous evidence that patients with known risk factors for thrombosis, such as aPL, might decrease their thrombosis risk by taking hydroxychloroquine; however, this association needs to be tested in prospective randomised controlled trials.

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Table 1

Characteristics of 1930 study participants with SLE

	n (%)
Females	1754 (91)
Ethnicity	
Caucasian	1119 (58)
Hispanic	262 (14)
Asian/Pacific Islander	227 (12)
African-American	202 (10)
Other (mixed ethnicity)	119 (6)
Age at study entry (mean, range in years)	42.1 (6-83)
Age at SLE diagnosis (mean, range in years)	32.8 (2-83)
Duration of SLE (mean, range in years)	9.1 (1-41)
Ever smoker	774 (40)
History of nephritis *	598 (31)
History of immunomodulator therapy [†]	1024 (53)
History of prednisone treatment	1654 (86)
History of hydroxychloroquine treatment	1534 (80)
History of NSAID [‡] treatment	1612 (84)
Number of subjects with	
≥1 thrombosis	426 (22)
≥2 thromboses	119 (6)
≥3 thromboses	32 (2)
Thrombosis by subtype	
Deep vein thrombosis	112 (20)
Pulmonary embolism	50 (9)
Cerebral vascular accident	98 (17)
Myocardial infarction	21 (4)
Retinal vein	13 (2)
Miscarriage in 1st trimester (3 consecutive)	5 (1)
Miscarriage late (≥1 in 2nd or 3rd trimester)	141 (25)
Other thromboses	124 (22)
Total thromboses	564
aPL positive (ACL or LAC) [§]	516 (27)
ACL positive	428 (22)
LAC positive	118 (6)
Thrombosis and aPL positive	187 (10)

ACL, anti-cardiolipin; aPL, antiphospholipid antibodies; LAC, lupus anticoagulant; NSAID, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

* Nephritis was defined as meeting American College of Rheumatology renal criterion, confirmed by review of medical records and/or renal biopsy consistent with lupus nephritis.

[†] Cyclophosphamide, azathioprine, methotrexate, ciclosporin, mycophenolate mofetil or chlorambucil.

[‡]All medications were analysed as: “ever” versus “never use”.

[§]aPL (ACL IgM or IgM or LAC (measured by Russell Viper Venom Time with confirmatory and mixing studies), positive at least once documented in records).

Table 2

Factors associated with one or more thrombosis events in bivariate analyses

Explanatory variables	OR (95% CI)	p Value
Female gender	0.88 (0.59 to 1.32)	0.498
Ethnicity		
Caucasian		
Hispanic		
African American		0.865 [†]
Asian/Pacific Islander		
Other (mixed)		
Age at SLE diagnosis (years)		
≤20	1.33 (0.80 to 2.23)	0.274
>20-≤40	1.27 (0.79 to 2.05)	0.325
>40	1.24 (0.75 to 2.04)	0.397
Duration of SLE (per 5 years)	1.21 (1.14 to 1.29)	0.013×10⁻⁷
Ever smoker	1.27 (1.00 to 1.60)	0.041
History of nephritis[‡]	1.62 (1.28 to 2.06)	0.0456×10⁻³
History of immunomodulator therapy[§]	1.52 (1.21 to 1.90)	0.0002
History of prednisone treatment	1.79 (1.21 to 2.73)	0.0029
History of hydroxychloroquine treatment	0.63 (0.48 to 0.83)	0.0007
History of NSAID treatment	1.00 (0.72 to 1.41)	0.997
aPL[¶]	2.79 (2.21 to 3.53)	<10⁻⁹
ACL positive	1.95 (1.47 to 2.58)	<10⁻⁹
LAC positive	3.35 (2.18 to 5.14)	<10⁻⁹

ACL, anti-cardiolipin; aPL, antiphospholipid antibodies; LAC, lupus anticoagulant; NSAID, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

* Significant results are shown in bold font.

[†] Omnibus test.

[‡] Nephritis was defined as meeting American College of Rheumatology renal criterion, confirmed by review of medical records and/or renal biopsy consistent with lupus nephritis.

[§] Cyclophosphamide, azathioprine, methotrexate, ciclosporin, mycophenolate mofetil or chlorambucil. All medications were analysed as “ever” versus “never use”.

[¶] aPL (ACL IgM or IgM or LAC (measured by Russell Viper Venom Time with confirmatory and mixing studies), positive at least once documented in records).

Table 3

Factors associated with one or more thrombosis events in multivariate analyses

Explanatory variable	≥1 Thrombosis OR (95% CI)	p Value	≥2 Thromboses OR (95% CI)	p Value	Test for trend p value
Female gender	-	-	-	-	-
Ethnicity	-	-	-	-	-
Ever smoker	1.26 (1.07 to 1.82)	0.011	1.90 (1.23 to 2.91)	0.004	0.012
History of nephritis*	1.35 (1.02 to 1.78)	0.036	1.65 (1.04 to 2.60)	0.033	0.000
Immunomodulator therapy [†]	1.40 (1.08 to 1.82)	0.011	1.95 (1.18 to 3.21)	0.009	0.000
Prednisone treatment	-	-	-	-	-
Hydroxychloroquine treatment	0.67 (0.50 to 0.90)	0.008	-	-	-
NSAID treatment	-	-	-	-	-
Age at SLE diagnosis					
≤20	0.52 (0.35 to 0.78)	0.001	-	-	-
>20-≤40	0.72 (0.54 to 0.97)	0.031	-	-	-
>40	-	-	-	-	-
Disease duration (per 5 years)	1.26 (1.17 to 1.35)	0.027×10⁻⁷	1.27 (1.12 to 1.43)	0.020×10⁻²	n/a
aPL [‡]	3.22 (2.49 to 4.16)	>10⁻⁹	5.05 (3.28 to 7.78)	0.020×10⁻¹¹	0.000

ACL, anti-cardiolipin; aPL, antiphospholipid antibodies; LAC, lupus anticoagulant; NSAID, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

* Nephritis was defined as meeting ACR renal criterion, confirmed by review of medical records and/or renal biopsy consistent with lupus nephritis.

[†] Cyclophosphamide, azathioprine, methotrexate, ciclosporin, mycophenolate mofetil, or chlorambucil. All medications were analysed as “ever” versus “never use”.

[‡] aPL (ACL IgM or IgG or LAC (measured by Russell Viper Venom Time with confirmatory and mixing studies), positive at least once documented in records).