Thrombosis in Systemic Lupus Erythematosus and Other Autoimmune Diseases of Recent Onset

JUANITA ROMERO-DÍAZ, ICELLINI GARCÍA-SOSA, and JORGE SÁNCHEZ-GUERRERO

ABSTRACT. ***Objective***. To determine the risk of thrombosis in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases of recent onset.

Methods. A retrospective cohort of 482 patients, mean age 28.3 years, with SLE or other autoimmune diseases was analyzed. Followup started at diagnosis or first appointment within 12 months since diagnosis until the development of thrombosis, end of study, loss to followup, or death. Thromboses were diagnosed upon clinical manifestations and confirmed by appropriate studies. Clinical variables were retrieved from the medical records, and SLE activity was assessed from the medical notes at onset of thrombosis, or at a dummy date for thrombosis, using the SLE Disease Activity Index-2K.

Results. During 2936 patient-years of followup, thromboses occurred in 49 patients (20.3%) with SLE and 6 patients (2.5%) with other autoimmune diseases. The incidence rate of thrombosis was 36.3 and 3.8 per 1000 patient-years in SLE and in other autoimmune diseases, respectively; relative risk 9.6 (95% CI 4.1–27.4, $p < 0.0001$). Throughout the disease course, the risk of thrombosis remained high in the SLE group, while in patients with other autoimmune diseases this risk was lower. The incidence of venous and arterial thrombosis was similar among SLE patients and patients with other autoimmune diseases. SLE and venous insufficiency were associated with thromboses in the total study population, and with venous insufficiency, vasculitis, and disease activity in the SLE group.

Conclusion. Patients with autoimmune diseases, particularly SLE, are at an increased risk of thrombosis. In patients with SLE, the risk remains elevated throughout the course of the disease. (First Release Nov 15 2008; J Rheumatol 2009;36:68–75; doi:10.3899/jrheum.071244)

Key Indexing Terms:
THROMBOSIS
SYSTEMIC LUPUS ERYTHEMATOSUS
AUTOIMMUNE DISEASES
INCIDENCE

Systemic lupus erythematosus (SLE) is an autoimmune disease with protean clinical manifestations that primarily affects young women. Although extraordinary improvement in the prognosis and survival rate has been accomplished[1,2], throughout the course of SLE disease patients deal with threats including disease activity, infections, irreversible organ damage, and severe clinical manifestations, i.e., thromboses, that impair their quality of life and survival rate[2].

The epidemiology of thrombosis has been studied in the Caucasian general population, showing that it is an unusual manifestation; in women age 30 years or less the incidence rate is 0.05 per 1000 person-years[3], and in postmenopausal women 0.08–0.11 per 1000 person-years[4-6]. Nevertheless, the incidence rate varies according to the health conditions of the population under study; among postmenopausal women with coronary heart disease the incidence rate increases to 4.3 per 1000 person-years[7], and in SLE, thrombosis occurs in up to 26% of patients[2,8-12].

Among prevalent SLE patients the incidence rate of thrombosis was 5.11 per 1000 patient-years[8], and in 2 inception cohorts it was 26.8[13] and up to 51.9 per 1000 patient-years, according to disease duration[10]. Along with the effects of irreversible damage, thrombosis is an independent risk factor for mortality[2,14,15].

In their pathogenesis, SLE and other autoimmune diseases share inflammatory mechanisms driven primarily by cytokines. Since inflammatory cytokines are the major mediators involved in activation of coagulation[16], we investigated whether the high risk of thrombosis observed in SLE is shared by other autoimmune diseases, and if the risk for venous and arterial thrombosis is different and if it varies during the course of the disease.

We describe the incidence rate of thrombosis during the

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Supported by grants CONACYT 3367P-M and 25556-M.

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Accepted for publication September 5, 2008.

disease course in patients with SLE and other autoimmune diseases of recent onset, the vascular territories affected, and the associated factors.

MATERIALS AND METHODS

Patients. A retrospective cohort study was conducted that included all the patients with a diagnosis of SLE of recent onset, defined as less than 1 year since diagnosis, attending our institute between January 1990 and December 2001. For each SLE patient, one patient with other autoimmune disease of recent onset was identified, matched by age (± 3 yrs), year of diagnosis (± 1 yr), and if possible, gender, to patients with SLE. SLE and other autoimmune disease diagnoses were made in accord with the American College of Rheumatology or other appropriate criteria[17-23], and the date of diagnosis was defined as the date the patient met the established number of criteria for classification/diagnosis of the corresponding disease. Patients with an episode of thrombosis of any kind previous to the study as well as those who were receiving anticoagulants for any reason were excluded.

Our institutional review board approved the study; signed informed consent was not required, since all information was collected from medical charts.

Followup period. All patients were followed from the time of the diagnosis of SLE or other autoimmune disease, or first appointment at the institute after the diagnosis until the onset of thrombosis, end of the followup period (December 31, 2006), loss to followup, or death, whichever came first. Patients who did not attend at least one scheduled visit to the institute within a year were censored.

Collected data. Medical records of all patients were reviewed by 2 physicians, using a standardized format to gather information about the development of thrombotic events and 48 variables, including: sociodemographic data (age, gender), comorbidities (antiphospholipid syndrome without thrombosis, diabetes mellitus, nephrotic syndrome, chronic obstructive pulmonary disease, hyperviscosity, dyslipidemia, venous insufficiency, systemic arterial hypertension, vasculitis, menopausal status, polycytemia, cancer, thrombotic thrombocytopenic purpura, congestive heart failure, myeloproliferative syndrome), gynoobstetric (pregnancies, miscarriages/stillbirths, deliveries), health-related behaviors (smoking), other known risk factors for thrombosis (recent surgery, immobilization for more than 7 days, use of hormonal contraceptives, menopause hormonal therapy), and treatment (prednisone, immunosuppressants, chloroquine/hydroxychloroquine, nonsteroidal antiinflammatory drugs especially low-dose aspirin). Height and weight at entry were recorded, and body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Among the patients with SLE, information was gathered about the date of diagnosis, age at diagnosis, disease duration at enrollment to the study, number and type of criteria accrued, and autoantibody profile (particularly antiphospholipid antibodies). Disease activity was assessed retrospectively from the clinical notes made by the treating physician, using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[24]. Abnormalities absent or not included in the medical record were considered as not present, and were scored as zero. To reduce the interphysician variability in these evaluations a training session and a calibration exercise in the scoring of the SLEDAI-2K were held, prior to the start of the study.

Main outcome. Incident venous or arterial thrombosis after the diagnosis of SLE or other autoimmune disease was the main outcome. Venous thromboses were defined as deep-vein thrombosis (venous circulation in the extremities or an internal organ) or pulmonary thromboembolism. Arterial thromboses were defined as stroke, myocardial infarction (MI), or internal organ or peripheral arterial thrombosis. A thrombosis was considered to occur when a patient developed clinical manifestations suggestive of such diagnosis and it was confirmed with at least one of the following studies: Doppler ultrasound, arterio/venography, V/Q pulmonary scintiscan, magnetic resonance imaging, computed tomographic scanning, or biopsy.

Study setting. The Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán is one of the Institutes of Health of México. It is a tertiary care center where most patients are admitted or referred for specialized care, due to complex diseases. The Department of Immunology and Rheumatology provides regular care to 6040 patients followed regularly, 85% with systemic autoimmune diseases, including almost 1780 with SLE.

Statistical analysis. Continuous variables were expressed as mean values and categorical variables as counts and percentages. Differences between groups were evaluated by the Student t test or Mann-Whitney U test, depending on the normality of data for continuous variables, and by chi-square or Fisher's exact test for categorical variables. Analysis of the incidence of thrombosis was based on incidence-density rates using patient-years of followup as the denominator and relative risk and 95% confidence intervals (95% CI) as the measure of association. We calculated the time for each subject from baseline until the development of thrombosis, discontinuation, end of followup, or death, whichever came first. Freedom from venous or arterial thromboses in patients with SLE or other autoimmune diseases was estimated using the Kaplan-Meier curve. The probability of thrombosis throughout the study was analyzed using life-table analyses and the log-rank test. Comparison of lupus activity was made calculating the SLEDAI-2K score at the date nearest the diagnosis of thrombosis or at a dummy date for thrombosis onset, chosen at random during the followup period among the patients who did not develop thrombosis. Factors associated with thromboses were analyzed separately for venous and arterial localization. To identify predictors for thromboses, clinically significant variables and those with p value $\leq$ 0.10 in the univariate analysis were included in the multivariable Cox proportional hazards model. p value was set as $\leq$ 0.05, and 2-sided p values are always reported. All analyses were done using Stata (Stata Corp., College Station, TX, USA), version 8.0.

RESULTS

From a population of 2141 patients with SLE, and 4098 patients with other autoimmune diseases, 241 with SLE and 241 with other autoimmune diseases (rheumatoid arthritis 156, dermato/polymyositis 24, scleroderma 23, thyroid disease 23, mixed connective tissue disease 7, seronegative spondyloarthropathy 7, primary Sjögren's syndrome 1) who met entry criteria were studied during 2936 patient-years of followup. Patients with SLE accrued 1349 and patients with other autoimmune diseases 1587 patient-years of followup. Demographic characteristics were comparable between both patient groups; however, SLE patients tended to be younger, and more females were included in this group. SLE patients also had more comorbidities (heart failure, arterial hypertension, and nephrotic syndrome) than patients with other autoimmune diseases (Table 1).

Incidence of thromboses. Fifty-five thromboses were observed during the study period, an incidence rate 18.7 per 1000 patient-years. Thromboses occurred in 49 patients (20.3%) with SLE and 6 (2.5%) with other autoimmune diseases [rheumatoid arthritis (RA) 3, dermatomyositis 2, ankylosing spondylitis 1]. The incidence rate of thrombosis was 36.3 per 1000 patient-years in the lupus population, and 3.8 per 1000 patient-years among the patients with other autoimmune diseases, relative risk 9.6 (95% CI 4.1–27.4, $p < 0.0001$). For RA, the incidence rate of thromboses was 2.9 per 1000 patient-years.

No difference was observed between the risk of venous and arterial thromboses in each patient group (Table 2).

Table 1. Demographic and comorbidity features in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases.

Variable	SLE, N = 241	Other Autoimmune Diseases, N = 241	p
Demographic features			
Age, yrs ± SD	27.7 ± 10.7	28.9 ± 10.7	0.06
Female, no. (%)	211 (88)	196 (81)	0.06
Body mass index, kg/m^2	22.8 ± 3.8	23.4 ± 4.1	0.13
Smoking ever, no. (%)	73 (30)	65 (27)	0.40
Comorbidity			
Diabetes mellitus, no. (%)	13 (5)	12 (5)	1.00
Neoplasias, no. (%)	5 (2)	4 (2)	1.00
Venous insufficiency, no. (%)	12 (5)	7 (3)	0.35
Dyslipidemia, no. (%)*	148 (69)	79 (74)	0.44
Heart failure, no. (%)	12 (5)	2 (1)	0.01
COPD, no. (%)	1 (1)	0	1.00
Arterial hypertension, no. (%)	86 (36)	23 (10)	< 0.0001
Nephrotic syndrome, no. (%)	55 (23)	2 (1)	< 0.0001

* Dyslipidemia was assessed among only 213 patients with SLE and 107 patients with other autoimmune diseases. COPD: chronic obstructive pulmonary disease.

Table 2. Incidence rates and type of thrombosis in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases.

Variable	SLE, N = 241	Other Autoimmune Diseases, N = 241	p
All thromboses, n	49	6*	
Incidence rate**	36.3	3.8	< 0.0001
Relative risk	9.6 (95% CI 4.1–27.4)		
Venous thromboses, n	25	4	
Incidence rate	18.5	2.5	< 0.0001
Relative risk	7.4 (95% CI 2.5–29.1)		
Arterial thromboses, n	24	2	
Incidence rate	17.8	1.3	< 0.0001
Relative risk	14.1 (95% CI 3.5–123.1)		

* Thromboses developed in rheumatoid arthritis 3 (incidence rate 2.9 per 1000 patient-yrs), dermatomyositis 2, and ankylosing spondylitis 1. ** Per 1000 patient-years.

Arterial localization involved in the SLE group were cerebral 21, coronary 2, and visceral 1; while in patients with other autoimmune diseases they were cerebral 1 and visceral 1. Venous thromboses among the SLE patients occurred in the lower limbs in 14, visceral 3, cerebral 2, or other locations 6, while in the patients with other autoimmune diseases the locations affected were lower limbs 2 and other 2.

No pregnancies occurred during the months preceding or at the time of diagnosis of thrombosis; however, a malignant neoplasia was diagnosed in one patient with SLE and in one with other autoimmune disease.

Clinical variables associated with thromboses. In the total study population, venous insufficiency, arterial hypertension, and a diagnosis of SLE were associated with the development of thrombosis ($p \leq 0.05$); however, in the multivariate analyses only venous insufficiency [hazard ratio (HR) 5.2; 95% CI 1.8–14.6], and a diagnosis of SLE (HR 11.2; 95% CI 3.9–31.8) remained statistically significant. When the risks for venous and arterial thromboses were analyzed separately, only diagnosis of SLE remained statistically significant (HR 6.4 and 16.8, respectively; data not shown).

Among patients with SLE, the variables associated with development of any kind of thromboses, and specifically venous and arterial thromboses, are shown in Table 3. In the multivariate analyses, venous insufficiency (HR 3.2; 95% CI 1.2–8.3), disease activity (HR 1.12; 95% CI 1.1–1.2), and vasculitis (HR 1.9; 95% CI 1.1–3.4) were associated with any kind of thromboses; while vasculitis (HR 2.5; 95% CI 1.1–5.6) and disease activity (HR 1.1; 95 CI 1.04–1.2) were associated with venous thromboses; finally, dyslipidemia (HR 2.8; 95% CI 1.2–6.8), central nervous system (CNS) manifestations (HR 5.2; 95% CI 2.0–13.9), and disease activity (HR 1.1; 95% CI 1.0–1.2) were associated with arterial thromboses.

Risk of thromboses in the course of SLE and other autoimmune diseases. In the SLE group, 78% of thromboses observed occurred during the first 5 years of followup; although all the venous thromboses developed within the first 6 years of lupus, the risk for developing arterial thromboses remained high throughout the course of the disease. Throughout the followup period, the relative risk of thromboses was higher among the patients with SLE than in the other autoimmune disease group. No defined pattern of occurrence was observed among the patients with other autoimmune diseases (Tables 4 and 5).

The Kaplan-Meier thrombosis-free survival analysis comparing patients with SLE and other autoimmune diseases is shown in Figure 1. It demonstrates the significantly lower probability of remaining thrombosis-free in SLE, during the course of the disease.

DISCUSSION

Our results show that patients with autoimmune diseases, particularly SLE, are at increased risk of developing thromboses. This risk remains high during the course of the disease in the patients with SLE, but a nondefined risk pattern is observed among the patients with other autoimmune diseases. SLE diagnosis was the single variable associated with venous and arterial thromboses in the whole study population, whereas among the patients with SLE venous thromboses were associated with vasculitis and disease activity, while dyslipidemia, CNS involvement, and disease activity were associated with arterial thromboses.

We studied a large population of patients with SLE and other autoimmune diseases, composed mostly of young women, within 1 year since diagnosis at the beginning of the followup period. Patients in both study groups were matched by age, year of diagnosis, and sex, and were followed during a similar length of time. Data on thromboses

Table 3. Variables associated with arterial and venous thrombosis among the SLE group. In the multivariate analyses, venous insufficiency (HR 3.2, 95% CI 1.2–8.3), disease activity (HR 1.12, 95% CI 1.1–1.2), and vasculitis (HR 1.9, 95% CI 1.1–3.4) were associated with any kind of thromboses; while vasculitis (HR 2.5, 95% CI 1.1–5.6) and disease activity (HR 1.1, 95% CI 1.04–1.2) were associated with venous thromboses; finally, dyslipidemia (HR 2.8, 95% CI 1.2–6.8), CNS manifestations (HR 5.2, 95% CI 2.0–13.9), and disease activity (HR 1.1, 95% CI 1.0–1.2) were associated with arterial thromboses.

Variable	No Thrombosis, n = 192	All Thrombosis, n = 49	Arterial Thrombosis, n = 24	Venous Thrombosis, n = 25	p*	p**	p†	p††
Duration of followup, yrs	6.2 ± 4.3	3.1 ± 3.2	4.6 ± 4.2	2.7 ± 2.4	< 0.001	0.07	< 0.0001	0.04
Duration at thrombosis or dummy date for thrombosis, yrs	2.0 ± 2.2	2.9 ± 2.9	3.6 ± 3.5	2.2 ± 2.0	0.08	0.04	0.57	0.10
Age at diagnosis, yrs ± SD	27.7 ± 10.5	27.8 ± 11.7	28.2 = 13.6	29.4 ± 12.5	0.75	0.35	0.72	0.44
Body mass index, kg/m^2	22.9 ± 4.0	22.2 ± 3.2	21.5 ± 3.3	23.1 ± 3.2	0.26	0.03	0.96	0.07
Smoking ever, n (%)	59 (31)	14 (29)	7 (27)	7 (24)	0.86	1.00	0.57	1.00
Pregnancies	1.4 ± 2.3	1.4 ± 1.6	0.81 ± 1.8	1.96 ± 2.6	0.79	0.08	0.13	0.09
Miscarriages/stillbirths	0.3 ± 0.6	0.2 ± 0.7	0.19 ± 0.5	0.32 ± 0.8	0.58	0.72	0.98	0.52
Diabetes mellitus, n (%)	13 (7)	0	0	0	0.10	0.39	0.39	1.00
Venous insufficiency, n (%)	7 (4)	6 (11)	3 (13)	2 (8)	0.07	0.09	0.28	0.67
Arterial hypertension, n (%)	69 (36)	17 (35)	11 (46)	6 (24)	1.00	0.38	0.27	0.14
Dyslipidemia, n (%)[a]	115 (68)	33 (77)	18 (90)	15 (65)	0.27	0.04	0.82	0.08
C-LDL (maximum)	152.3 ± 65.7	155.9 ± 118.4	129.0 ± 35.3	182.9 ± 165.6	0.27	0.36	0.53	0.42
C-HDL (minimum)	42.8 ± 22.9	36.6 ± 19.2	31.4 ± 18.1	41.7 ± 19.8	0.27	0.13	0.89	0.24
CNS involvement, n (%)	34 (18)	18 (37)	13 (54)	5 (20)	0.006	< 0.0001	0.78	0.02
Anticardiolipin ab, n (%)[b]	87 (62)	20 (63)	13 (76)	7 (47)	1.00	0.29	0.27	0.14
Anti-ß$_2$ GPI ab, n (%)[c]	26 (41)	10 (67)	5 (71)	5 (63)	0.09	0.23	0.28	1.00
Nephrotic syndrome, n (%)	46 (24)	9 (18)	4 (15)	5 (17)	0.45	0.52	0.36	1.00
Low-dose aspirin, n (%)	32 (17)	6 (12)	2 (8)	4 (14)	0.52	1.00	0.29	0.67
Chloroquine, n (%)	63 (33)	13 (27)	3 (12)	10 (34)	0.49	0.03	0.84	0.06
APS, n (%)	13 (7)	10 (20)	6 (23)	4 (14)	0.01	< 0.0001	0.02	0.49
SLE criteria	6.1 ± 1.7	6.6 ± 1.6	6.9 ± 1.6	6.2 ± 1.6	0.19	0.04	0.91	0.09
Vasculitis, n (%)	54 (28)	26 (53)	12 (46)	14 (48)	0.002	< 0.0001	< 0.0001	1.00
SLEDAI at thrombosis or dummy date for thrombosis[d]	4.0 ± 4.1	7.3 ± 5.8	7.5 ± 5.4	7.2 ± 6.2	0.0001	0.002	0.01	0.61

* Between patients without thrombosis and patients with thrombosis. ** Between patients without thrombosis and patients with arterial thrombosis. † Between patients without thrombosis and patients with venous thrombosis. †† Between patients with arterial thrombosis and patients with venous thrombosis. [a] Dyslipidemia was assessed only among 170 SLE patients without thrombosis and 43 SLE patients with thrombosis. [b] Anticardiolipin antibody was determined only among 140 SLE patients without thrombosis and 32 SLE patients with thrombosis. [c] Anti-ß$_2$-GPI antibody was determined only among 64 SLE patients without thrombosis and 15 SLE patients with thrombosis. [d] Among patients who did not develop thrombosis, a random date during the followup was selected. LDL: low density lipoprotein; HDL: high density lipoprotein; CNS: central nervous system; ab: antibody; APS: antiphospholipid syndrome; GPI: glycoprotein I; SLEDAI: SLE Disease Activity Index; HR: hazard ratio.

Table 4. Incidence rate (per 1000 patient-years) of thromboses throughout disease course.

Year	All Thromboses, SLE	All Thromboses, Other AID	Patient-yrs SLE	Patient-yrs Other AID	Incidence Rate, SLE	Incidence Rate, Other AID	RR
1	16	0	212.8	207.8	75.2	0	—
2	8	1	183.3	183.8	43.6	5.4	8.1
3	6	0	165.6	172.8	36.2	0	—
4	3	0	153.4	162.3	19.6	0	—
5	5	1	141.3	148.7	35.4	6.7	5.3
6	4	0	120.9	137.4	33.1	0	—
7	2	1	93.4	121.3	21.4	8.2	2.6
8	1	0	67.7	105.9	14.8	0	—
9	0	1	50.8	84.6	0	11.8	—
10	1	1	41.3	69.4	24.2	14.4	1.7
11	2	0	34.7	57.8	57.6	0	—
12	0	0	27.2	44.0	0	0	0
> 12	1	1	56.3	88.0	17.8	11.4	1.6
Total	49	6	1348.7	1586.7	34.8	3.8	9.2

SLE: systemic lupus erythematosus, AID: autoimmune diseases, RR: relative risk.

Table 5. Incidence rates (per 1000 patient-years) of arterial and venous thrombosis among the SLE patients according to duration of disease.

Year	Arterial Thromboses	Venous Thromboses	Patient-yrs	Incidence Rate, Arterial	Incidence Rate, Venous	RR
1	7	9	212.8	32.9	42.3	0.8
2	6	2	183.3	32.7	10.9	3.0
3	2	4	165.6	12.1	24.2	0.5
4	1	2	153.4	6.5	13.0	0.5
5	2	3	141.3	14.2	21.2	0.7
6	2	2	120.9	16.5	16.5	1.0
7	2	0	93.4	21.4	0	—
8	1	0	67.7	14.8	0	—
9	0	0	50.8	0	0	—
10	1	0	41.3	24.2	0	—
≥ 11	3	0	34.7	86.4	0	—

RR: relative risk.

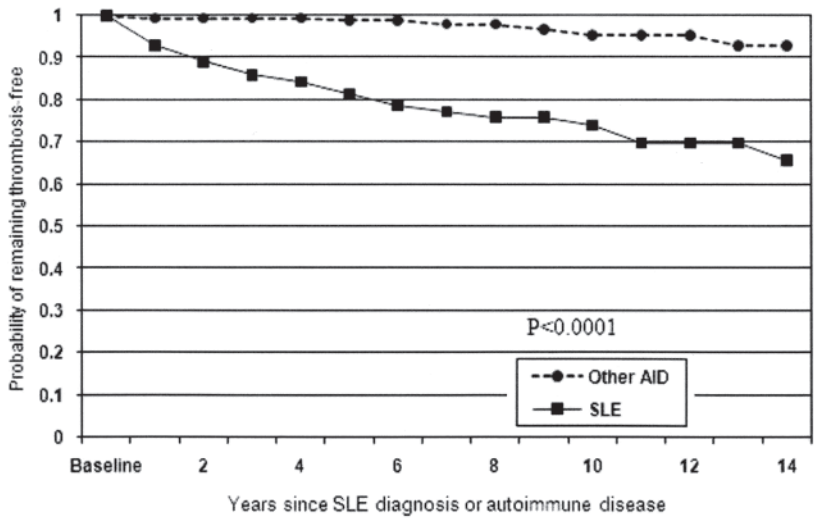

Figure 1. Kaplan-Meier curve for thrombosis-free survival. The probability of remaining thrombosis-free is significantly lower in patients with SLE than in patients with other autoimmune diseases (AID).

and associated clinical variables were abstracted from medical records; thromboses were diagnosed in all the patients upon the presence of suggestive clinical manifestations and confirmed with appropriate studies.

The incidence rate of thromboses observed in both patient groups was much higher than that reported among pre- and postmenopausal Caucasian women[3-6]. Even more, in the group with other autoimmune diseases, particularly those with RA, the incidence rate was similar to that reported among postmenopausal women with coronary heart disease[7], and among patients with SLE this figure was even higher.

Although patients with other autoimmune diseases have an elevated incidence of thromboses, patients with SLE are at a much higher risk. This finding is interesting, since inflammatory mechanisms underlie the pathogenesis of SLE and other autoimmune diseases; and in SLE and RA patients there is also a high incidence of cardiovascular events, not explained by traditional cardiac risk factors[25,26]. Therefore, other factors that contribute to the increased risk of thrombosis in SLE remain to be defined.

Our results are consistent with the incidence rates reported in 2 SLE inception cohorts, 26.8 per 1000 patient-years from a multiethnic cohort[13] and up to 51.9 per 1000 patient-years in a cohort composed mostly of Caucasian patients[10]; and 16.0 per 1000 patient-years among 144 consecutive SLE patients[9], and 19.5 per 1000 patient-years among 425 SLE patients[12]. No information for the incidence rate of thromboses has been reported for other autoimmune diseases; our results seem to be the first estimation available.

Although most thromboses in patients with SLE devel-

oped within the first 5 years of disease, the risk for arterial thromboses remained high throughout the course of the disease. Although venous and arterial thromboses occurred with similar frequencies, venous thromboses took place during the early years of disease, while arterial thromboses developed throughout the study period. Other studies have also reported that the risk for thrombosis is highest within the first 5 years from diagnosis of lupus[10,11], and the trend observed for venous and arterial thrombosis throughout the course of the disease was also reported in another inception cohort of lupus patients[10]. Among the patients with other autoimmune diseases the frequency of venous and arterial thromboses was also similar; however, their onset did not show a defined pattern and occurred throughout the followup period.

Thrombosis has been reported in about 10% of prevalent patients with SLE[8]. In our study 20.3% of the SLE patients developed a thrombotic event, similar to the 16.2% observed in another inception cohort[10], 20.1% reported among 144 consecutive patients[9], and 26.3% among 426 patients[12]. The higher percentage observed in inception cohorts reflects the risk of thrombosis during the early years of the disease.

Thromboses in patients with SLE may result from diverse mechanisms, including inflammatory, primarily thrombotic, or atherosclerotic. The relevance of each mechanism may vary throughout the course of the disease, thus atherosclerosis seems to predominate late in the evolution of the disease[27]. We observed 2 MI in our lupus cohort, one male age 31 years and one female patient 43 years of age, with SLE duration of 93 and 117 months, respectively, at the onset of MI. The incidence rate of MI observed in our study, 1.48 per 1000 patient-years, is significantly lower than the rate reported in another cohort of women with SLE, 6.53 per 1000 patient-years (incidence rate ratio 0.23, 95% CI 0.03–0.92)[28]. The low rate of MI observed in our study may derive from the characteristics of the population studied.

Several variables, i.e., smoking, age, disease activity, lupus anticoagulant, dose of glucocorticoids, disease duration, male sex, ethnicity, dyslipidemia, obesity, and diverse lupus manifestations, have been associated with the risk of thrombosis in patients with SLE[8,10,11,13,29]. In our study, vasculitis and disease activity were associated with venous thromboses, while dyslipidemia, CNS manifestations, and disease activity were associated with arterial thromboses. The latter variable deserves emphasis because it reflects an ongoing inflammatory process as a relevant pathophysiologic mechanism for venous and arterial thromboses in SLE. This result is consistent with the higher disease activity at baseline and higher average disease activity over time observed among the patients who developed thromboses in another inception cohort[10], as well as in a multiethnic cohort[11]. This hypothesis has biological support, since inflammatory cytokines are the major mediators involved in coagulation activation. Inflammatory mediators can elevate platelet count, platelet reactivity and fibrinogen concentration, downregulate natural anticoagulant mechanisms, initiate the coagulation system, facilitate propagation of the coagulant response, and impair fibrinolysis[16]. The interactions between inflammation and coagulation may explain the higher rate of thromboses during the early years of SLE, when disease activity in general is higher than later during the disease course, and also may explain the variability in the incidence rate of thromboses observed in diverse health conditions.

We did not observe an association of thromboses with antiphospholipid antibodies. Nevertheless, SLE patients who met the criteria for antiphospholipid syndrome, except thromboses, at the start of the study did develop thromboses more often during the followup. Given the robustness of this subgroup of patients, the lack of association with antiphospholipid antibodies may be explained because this laboratory test was not performed in every patient, as discussed below.

Our study has several potential limitations. Although it is a retrospective cohort study, thrombosis is a hard outcome that is difficult to overlook and it was strictly diagnosed; thus we are confident that the patients identified with thrombosis truly developed it and that our estimate of the incidence rate is reliable. However, we should acknowledge that clinicians are sensitive to the occurrence of thrombosis in young patients with SLE, but the situation may not be similar with other autoimmune diseases, therefore some underestimation of the incidence rate of thrombosis among patients with other autoimmune diseases might have occurred. On the other side, the incidence of some less symptomatic thrombotic episodes could be higher in patients with SLE. If these ascertainment biases had happened, the relative risk for thrombosis reported among SLE patients in comparison with patients with other autoimmune diseases would be overestimated in the former scenario and underestimated in the latter situation. However, we consider both situations unlikely, given the robustness of thrombosis as an outcome.

Given the reduced number of patients with specific diseases in the other autoimmune disease group, except for RA, we could not obtain a stable estimate of the incidence rate of thromboses for each disease.

Although the investigators carefully extracted the variables associated with thromboses, they were limited to the evidence of each variable in the medical chart. In addition, not every laboratory test was performed in each patient. This situation is reflected by the lack of association between thromboses and antiphospholipid antibodies. Therefore one should be reserved about some of these results since some misclassification might be present.

Disease activity was not systematically assessed in patients with other autoimmune diseases as in the SLE group. Therefore, although the different incidence of throm-

boses between the 2 groups might be partially explained if inflammation were systematically lower in patients with other autoimmune diseases than in SLE, we consider this situation unlikely since both groups were matched by disease duration.

Genetic thrombophilic defects were not systematically assessed in our study population; therefore, it remains unknown whether a dissimilar distribution of inherited thrombophilic defects between patients with SLE and other autoimmune diseases might explain the different incidence of thromboses.

The incidence density rate of thrombosis in patients with SLE and other autoimmune diseases was compared with figures reported in studies in Caucasian populations, because there is little information from Hispanic and specifically Mexican populations.

Our study was conducted in a tertiary care center where patients with more severe disease and probably at a higher risk of thrombosis are seen. Therefore, our estimates may not apply to patients with SLE and other autoimmune diseases followed in general medical settings.

Some strengths of our study also need to be considered. All the thromboses reported occurred after the diagnosis of SLE or other autoimmune disease during the followup at our institution. We included patients with SLE and other autoimmune diseases of recent onset, which allowed us to compare the incidence rate of thromboses in both patient groups as well as the risk throughout the course of the diseases. All our patients were Mexican; since it has been shown that there are ethnic differences in the incidence of arterial and venous thromboses in patients with SLE[13], our study provides a reliable estimate for Hispanic patients.

Based on the results reported, we may conclude that patients with autoimmune diseases, particularly SLE, are at an increased risk of developing venous and arterial thromboses. SLE is among the highest acquired-risk factors for thromboses in young people, and the risk remains increased throughout the progress of the disease.

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