Infections Increase Risk of Arterial and Venous Thromboses in Danish Patients with Systemic Lupus Erythematosus: 5102 Patient-years of Followup

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*ABSTRACT. **Objective.*** Infections and thromboses are known complications of systemic lupus erythematosus (SLE). We investigated if infectious episodes in patients with SLE were followed by an increased risk of thrombotic events.

Methods. A cohort of 571 patients with prevalent or incident SLE was followed for a mean of 8.9 ± 7.6 years. All episodes of hospitalized infections or episodes of cutaneous herpes zoster as well as arterial and venous thrombotic events were identified by retrospective chart review and prospective updating of a clinical database. For time-dependent analyses adjusted for age, sex, and ever-presence of antiphospholipid antibodies, thrombotic events were classified as occurring during the time at risk of 1 year after an infection or during the remaining control observation time.

Results. Of 271 infections identified, 104 were respiratory, 41 cutaneous herpes zoster, and 126 others. Of 159 thromboses identified, 98 were arterial. Incidence for arterial and venous thromboses within 1 year after infection was 2.18% and 2.56%, respectively, compared to patients who never had an infection (0.58 and 0.67). The adjusted 1-year risk of arterial and venous thrombosis after any infection was increased [relative rate (RR) 2.5, 95% CI 1.4–4.6, and RR 2.8, 95% CI 1.3–5.9, respectively]. Venous thromboses were in particular more prevalent after respiratory infections (RR 5.4, 95% CI 2.3–13).

Conclusion. The temporal associations observed in this study indicate that infections could be risk factors for arterial or venous thromboses in patients with SLE, although causality was not addressed by this study. (J Rheumatol First Release Aug 15 2014; doi:10.3899/jrheum)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS THROMBOSIS INFECTION

Infections and thromboses occur at an increased rate in patients with systemic lupus erythematosus (SLE) and, together with active SLE, are the most frequent causes of death in patients with SLE[1,2,3]. In general, acute infections have been recognized to be associated with the development of arterial thromboses, including myocardial infarction (MI) and stroke[4]. Also, the risk of MI and stroke after an acute respiratory tract infection is greater than after less severe urinary tract infection[5]. Large retrospective studies consistently find a 2-fold to 3-fold increase in the risk for acute coronary syndromes within 1–2 weeks after a respiratory infection, and this risk remains significant at 3 months[4]. It has been hypothesized that infections, in addition to eliciting systemic inflammatory responses, can also have direct inflammatory effects on atherosclerotic plaques and coronary arteries[4]. Studies have also demonstrated that there is a transient (up to 1 year) increased risk of venous thromboses [deep venous thrombosis (DVT) and pulmonary embolism (PE)] after respiratory infection[6,7] and urinary tract infection[7] in the general population. Clayton, *et al* found a 2.6-fold increased risk of DVT in the month following a respiratory infection persisting up to a year, as well as a 2.5-fold increased risk of PE for the same period[6].

We investigated whether infectious episodes in patients with SLE were followed by an increased risk of arterial and venous thrombotic events.

MATERIALS AND METHODS

Patients and procedures. Our SLE cohort was started and the majority of data (on 513 patients) were retrospectively collected in 1995 as part of previous study[8]. Patients were followed at several hospital centers in Denmark, including university hospitals that have specialized functions in diagnosing and treating SLE, and locally identified by means of a national disease coding system. Data collection on consecutive patients with SLE seen at one of the university hospitals is continuing, and we included further incident cases, resulting in data on 571 adult patients with SLE fulfilling the modified American College of Rheumatology (ACR) 1982[9] or 1997[10] classification criteria. The electronic SLE database includes basic demographics, SLE symptoms and dates of symptom onset, immunologic

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results, date of diagnosis, length of followup, and details on occurrence of infections and thrombotic events. The database is anonymous and was approved by Danish ethics agencies.

For study purposes, the start of followup for each patient was the date when SLE classification was achieved, and the end of followup was date of death or most recent information recorded. These data were provided by data extractors from each participating center and subsequently entered into the database. The same data extractors were obtaining the data on risk factors and outcomes (thrombosis and infections) for each patient; however, in all instances without knowledge of the hypothesis of the present study. A standard approach was based on a predefined data collection form to retrospectively extract data from each patient's hospital or outpatient chart. All records including discharge summary were reviewed. In the majority of cases the information was extracted retrospectively, and in some cases followup data as per routine patient care were included prospectively. The frequency of followup visits for these patients was not affected by the study.

All infectious events requiring or occurring during hospitalization, events of cutaneous herpes zoster, and arterial and venous thrombotic events had been identified. Infections requiring or occurring during hospitalization due to SLE flares or other reasons were classified into 2 groups: (1) respiratory and (2) other infections, such as urinary tract, gastrointestinal, gynecological, cerebral, cutaneous infections, bacteremia, and other (not specified) infections. The respiratory infection group included pneumonias and pulmonary abscesses. The third group of infections for study purposes was cutaneous herpes zoster. Diagnosis of an infection was made by the treating physician based on clinical symptoms, laboratory tests (including microbiological analysis of sputum, blood, and other when indicated), and imaging studies as per standard of care.

Venous thrombotic events included DVT, PE, retroperitoneal thrombosis, and thrombosis in the veins of the neck and eyes diagnosed on clinical symptoms and relevant imaging studies [ultrasound, phlebography, diffusion/perfusion scan, or computed tomography (CT)]. Arterial thrombotic events included stroke, MI, and spleen, kidney and other arterial thrombotic events, diagnosed on clinical symptoms, laboratory results (troponin levels), electrocardiogram findings, relevant imaging studies (CT, magnetic resonance scans, echocardiography), or autopsy findings.

When patients with SLE are hospitalized at local hospitals due to infections, thromboses, or SLE flares, it is common practice in Denmark to transfer these patients to university hospitals, ensuring a high degree of coverage of information on all infectious and thrombotic events for the patients included in the study.

Statistical analysis. Statistical analyses were performed using SPSS 18.0. Incidence rates were calculated by relating the number of events of interest (arterial or venous thrombosis) among patients who had an infection to the accumulated number of patient-years during defined intervals after an exposure (infection), in this study referred to as time at risk (TAR; Figure 1) and compared with the incidence rates in patients who never had an infection.

The TAR was defined as 1 year after an infection and was subdivided into periods of 3, 6, and 12 months. Thrombotic events were classified as occurring during TAR of 12 months or control observational time. The end of the control observation time (COT; followup) was the date of death or the last information recorded in the database. The null hypothesis was that thrombotic event rates remain constant and are not affected by an exposure to an infection. Thus both exposed and unexposed cases were included in the analyses. Poisson regression analysis was used to estimate adjusted relative risks (RR) and 95% CI and allowed adjustment for age, sex, and ever-presence of antiphospholipid antibodies (aPL).

RESULTS

Of 571 patients studied, 89% were female, with a mean age at diagnosis of 36.7 ± 16 years (Table 1). Patients were followed for a total of 5102 years and the mean length of followup was 8.9 ± 7.6 years. In 321 (40.4%) patients, aPL, [anticardiolipin antibodies (IgG/IgM isotypes)], lupus anticoagulant, or a false-positive Wassermann reaction had been detected at some point during followup as part of routine care.

Infections as defined in this study occurred 271 times in 173 patients, equivalent to 5.3% infections per year. Among these, 104 (38%) were respiratory, 41 (15%) cutaneous herpes zoster, and 126 (47%) other acute infections (Table 1). A total of 159 thromboses were identified in 112 patients, equivalent to 3.1% thromboses per year. Of those, 62% were arterial, predominantly stroke (48%) and MI (40%; Table 1). Twelve arterial thromboses occurred during the TAR of 12 months following an infection and 86 during COT. Arterial thromboses occurring during this TAR included 5 MI, 6 strokes, and 1 other. Respiratory tract infections were followed by 2 MI, 2 strokes, and 1 other arterial thrombosis; herpes zoster by 1 MI and 1 stroke; and other infections by 2 MI and 3 strokes. Arterial thromboses occurring during COT included 34 MI, 41 strokes, and 11 other thromboses (spleen, kidney, and other). There was no difference in the distribution of type of arterial thromboses during TAR and COT (chi-square test, $p = 0.87$).

Eight venous thrombotic events occurred during the TAR of 12 months: 6 after respiratory tract infections and 2 after other infections. No venous thromboses after cutaneous herpes zoster infections were identified. Fifty-three venous thrombotic events occurred during COT: 70% were DVT, 13% PE, 4% retroperitoneal thrombosis, and 4% other thromboses. Five events were both DVT and PE. Interestingly, the majority (87.5%) of venous and about half (58%) of arterial thrombotic events occurred within 6 months following an infection.

During followup of the 571 patients, 346 patients had neither infections nor thromboses, while infections, thromboses, or both were observed in 113, 52, and 60 patients, respectively. These figures led to an odds ratio of 3.5 (95% CI 2.3–5.5), demonstrating a non-time-dependent association between thromboses and infections. However, a time-dependent association (within 1 year after an infection) was also observed between infections and arterial and venous thrombotic events (Table 2). For arterial thromboses, the incidence rates per 100 patient-years during TAR of 0–3, 3–6, and 6-12 months were 4.16, 8.25, and 4.95, respectively, compared to 1.45 among patients who never had an infection. Outside TAR (12 + months) the incidence rate was 2.48. The incidence rate ratio was only significantly increased for TAR of 0–12 months compared to patients who had never had an infection (2.18, 95% CI 1.13–3.81). For venous thromboses, the incidence rates per 100 patient-years during TAR of 0–3, 3–6, and 6–12 months were 6.93, 4.12, and 0.99, respectively, compared to 0.94 among patients who never had an infection. Outside TAR (12 + months) the incidence rate was 1.41. The incidence

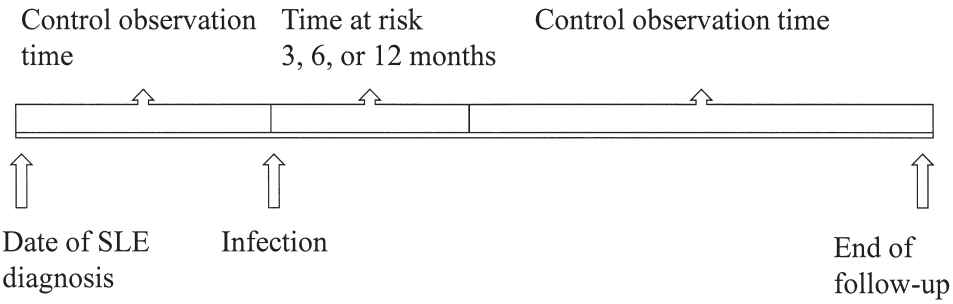

Figure 1. A sample of distribution of control observation time and time at risk in a patient with systemic lupus erythematosus (SLE). This patient had 1 infectious episode during followup. The length of followup for each patient was defined as time from the date when SLE was diagnosed until the end of followup (death or the last information recorded in the database). The length of the control observation time varied for different patients and included time both before and after an infection. Some patients had no infections; the control observation time for these patients was equal to the length of followup. Time at risk was defined as 1 year following an infection, and was subdivided into periods of 3, 6, or 12 months for time-dependent analyses.

Table 1. Basic characteristics of 571 patients with systemic lupus erythematosus and infections and thromboses observed during mean followup of 8.9 years.

Characteristic	
Male:female ratio	9:1
Age at diagnosis, yrs, mean (range)	36.7 ± 16 (9–82)
Length of followup, yrs, mean (range)	8.9 ± 7.6 (1 mo–64 yrs)
Total yrs of followup	5102
aPL ever, n (%)	231 (40.4)
Thromboses, n	
Arterial	98
Myocardial infarction	39
Stroke	47
Other (spleen, kidney, and other)	12
Venous	61
PE	9
DVT	42
DVT and PE	6
Retroperitoneal thrombosis	2
Other (veins in the neck and eyes)	2
Infections, n	
Respiratory	104
Pneumonia	103
Other respiratory infections (pulmonary abscess)	1
Cutaneous zoster	41
Other infections (requiring hospitalization)	126
Bacteremia/sepsis	27
Urinary tract infection	23
Not specified	20
Gastroenteritis	12
Bacterial skin infection	11
Meningitis	6
Sinusitis	4
Subcutaneous abscess	4
Abscess, other location	3
Salpingitis	3
Viral hepatitis	3
Septic spondylitis	3
Retroperitoneal abscess	2
Septic arthritis	1
Endocarditis	1
Peritonitis	1
Epididymitis	1
Otitis media	1

aPL: antiphospholipid antibodies; PE: pulmonary embolism; DVT: deep venous thrombosis.

rate ratios were significantly increased for TAR of both 0–3 and 0–12 months compared to patients who never had an infection, and the incidence rate ratio was numerically higher for the period of 0–3 months compared to the 12-month period (Table 2).

Risks of thromboses during the 12-month TAR after adjustment for age, sex, and aPL are given in Table 3, showing that aPL and male gender were associated with development of both arterial and venous thromboses. Advanced age was associated with increased risk of arterial (RR 1.4, 95% CI 1.2–1.6) but not venous thrombosis. Any infection was associated with increased risk for development of both arterial and venous thromboses independently of presence of aPL (RR 3.1, 95% CI 1.7–5.6, and RR 3.3, 95% CI 1.6–7.0, respectively). For development of arterial thrombosis the RR was similar for the various categories of infections we studied, although a significantly increased RR was seen only after respiratory infections, which was also the case for venous thrombosis (Table 3).

DISCUSSION

Our study suggests that patients with SLE are at increased risk of developing thromboses within 1 year after infections. The study demonstrated that SLE patients are 2.5–3 times more likely to develop an arterial and venous thrombosis within 12 months after an infection requiring or occurring during hospitalization or cutaneous zoster episodes. Venous thromboses in particular were more prevalent following a respiratory infection, and the risks of arterial thromboses were similar following all 3 infection groups studied, although most significantly after respiratory infections. To our knowledge, this is the first study describing such associations between infections and thromboses in patients with SLE.

Previous studies in the general population demonstrated that risk of MI and other thromboses is increased after an infection. In patients with SLE, possible mechanisms in

Table 2. Incidence rates and corresponding incidence rate ratios of arterial and venous thromboses during the time at risk (TAR) within 3, 6, and 12 months after an infection and 12+ months among patients who had had an infection, compared to the patients who had never had an infection.

	Events, n	Observation Time, yrs	Incidence Rate, %/yr	Incidence Rate Ratios Relative to TAR 12+ (95% CI)	Lower Limit	Upper Limit
Arterial thromboses						
Never infected	49	3387.8	1.45	0.58	0.42	0.83
TAR 0–3 mo	3	72.2	4.16	1.68	0.35	4.90
TAR 3–6 mo	4	48.5	8.25	3.33	0.91	8.52
TAR 6–12 mo	5	101.1	4.95	2.00	0.65	4.66
TAR 0–12 mo	12	221.8	5.41	2.18	1.13	3.81
TAR 12+ mo	37	1492.8	2.48			
Venous thromboses						
Never infected	32	3387.8	0.94	0.67	0.44	1.09
TAR 0–3 mo	5	72.2	6.93	4.93	1.60	11.49
TAR 3–6 mo	2	48.5	4.12	2.93	0.36	10.59
TAR 6–12 mo	1	101.1	0.99	0.70	0.02	3.92
TAR 0–12 mo	8	221.8	3.61	2.56	1.11	5.05
TAR 12+ mo	21	1492.8	1.41			

Table 3. Risk ratios of arterial and venous thromboses (occurring within 12 months after an infection) by infections, including subsets adjusted for age, sex, and presence of antiphospholipid antibodies (aPL), at some time during the observation period, in 571 patients with systemic lupus erythematosus followed for a mean of 8.9 years.

	Arterial Thromboses, RR (95% CI)	Venous Thromboses, RR (95% CI)
Age, per decade	1.4 (1.2–1.6)	1.0 (0.86–1.2)
Male sex	2.2 (1.4–3.7)	3.5 (2.0–6.2)
aPL ever	1.7 (1.1–2.6)	1.8 (1.1–3.0)
Any infection	2.5 (1.4–4.6)	2.8 (1.3–5.9)
Subsets of infections*		
Respiratory	2.4 (1.0–5.9)	5.4 (2.3–13)
Cutaneous zoster	2.6 (0.64–11)	0 (not calculated)**
Other	2.1 (0.83–5.1)	1.3 (0.31–5.2)

*Adjusted for age, sex, and aPL ever. **No event of venous thrombosis occurred in this specific subset. RR: relative risk; CI: confidence interval.

development of thromboses are immune complex-mediated vessel injury/vasculitis, premature atherosclerosis, presence of aPL, acquired protein S deficiency, microparticles[11], and innate immunity factors (e.g., homozygosity for mannose-binding lectin variant alleles for development of arterial thromboses[12]).

In our study, 40.4% of patients were aPL-positive at some point during followup as part of their routine care. This rate is similar to that found in other SLE cohorts[13,14]. As expected, patients in whom aPL had been detected at some time during followup were at increased risk of developing both arterial and venous thromboses. A shortcoming of our study is the lack of continuous monitoring of aPL during followup of this cohort. Thus, we cannot exclude a temporary upregulation of aPL during or after an infection. However, we believe that any such upregulation/seroconversion is more likely to occur in patients who at some point were positive for aPL than in those who had been negative for aPL. Nevertheless, in our cohort, having an infection, independent of infection type, was associated with increased risk for development of both arterial and venous thromboses independent of observation of aPL. Further, in time-dependent analyses we found differences in RR adjusted for age, sex, and ever-presence of aPL for development of arterial and venous thromboses following different infection types: during the mean followup of 8.9 years the patients were 2.5 times more likely to develop arterial thromboses after respiratory, cutaneous zoster, and other infections; however, in cases of venous thrombosis the risk was increased 5.5 times after respiratory infections and was not associated with other infections. These findings indicate the presence of various pathogenetic mechanisms, and also some that are not associated with presence of aPL.

For this time-dependent adjusted analysis we selected 12 months following an infection as the time at risk to include most outcome events (thromboses) in order to increase statistical power, and it was also during this time interval that incidence rate ratios were significantly increased for both arterial and venous thromboses compared to the control observation time. This approach is supported by studies that have demonstrated a transient, up to 1-year increased risk of venous thromboses (DVT and PE) after a respiratory infection and urinary tract infection in the general population[6].

A limitation of the study is that we did not have data on and thus could not adjust for all relevant modifiers of thrombotic risk, e.g., comorbidities such as hypertension, diabetes, peripheral vascular disease, or hematological conditions or hypercoagulable states, as well as medications and disease activity. In addition, as only infections requiring or occurring during hospitalizations were included in this study, any immobilization of the patients could also cause a bias toward thrombotic events.

Our results also demonstrated an overall (not time-dependent) association between thromboses and infections. This may suggest the existence of common mechanisms for development of both infections and thromboses, such as mannose-binding lectin deficiency, which has been associated with both arterial thromboses and infection in SLE[12,15]. However, our time-dependent analyses indicate that the association between infections and thromboses we observed are due at least in part to direct effects of infection on development of thromboses, without the confounding effect of overlying mechanisms. However, given the incidence of thromboses and infections of 3% and 5% per year, respectively, in this cohort, and given the adjusted RR ranging from 2.1 to 5.4, infections in patients with SLE seem in absolute terms to confer only a moderate risk of thromboses. In our view this finding alone does not justify changing treatment algorithms in the management of SLE. However, it should be noted in particular that the increased risk of venous thromboses following respiratory infections observed in our cohort corresponds to the increased risk of venous thromboses following respiratory infections in the general population. On the agenda for future research we include further examination of such risk in other larger cohorts or national discharge registries allowing more certain risk estimates and further stratifications.

Age was associated with increased risk of arterial but not venous thrombosis. This may very well reflect an expected increase of atherosclerosis with increasing age. Interestingly, in our study male sex was associated with development of both arterial and venous thromboses. In a recent study of 743 SLE patients this was also observed for thromboses and strokes in general[16]. Another study demonstrated that male sex was a significant predictor of thrombosis (arterial and venous) in SLE patients, irrespective of their aPL status[17]. Studies have demonstrated that in the general population as well, risk of recurrence of venous thrombosis (DVT and PE) is increased in men compared with women[18,19]. The high recurrence rate in men compared with women was still observed when only patients with idiopathic venous thrombosis were analyzed[19]. The mechanisms for this association could not be addressed in our study.

The incidence of thromboses in our study was close to that observed in other studies. In the "Euro lupus" project a cumulative incidence rate of thrombotic events was 9.2% in 1000 patients with SLE followed over 10 years[2]. Brouwer, *et al* reported incidence rates of 10% for venous thrombosis and 11% for arterial thrombosis in a study of 144 patients with SLE with a median followup of 12.7 years[20]. In the Toronto study cohort, a total of 544 patients followed for a median duration of 6.3 years, 16% had a thrombotic event after diagnosis of SLE, which equals a rate of 2.5% per year[21], close to the 3.1% per year rate observed in this study. In the Johns Hopkins Lupus Cohort of 678 patients, the rate of first-time venous thrombosis was about 0.5% per year[22], and the corresponding rate in our study was 0.8% per year.

We found that 30% of patients in our study had at least 1 infectious episode, similar to the rates observed in other studies ranging from 14% to 77%[23,24,25], and in most studies reported as up to 50%[26].

Our study demonstrates for the first time the temporal associations indicating that infections could be relevant risk factors for arterial or venous thromboses in patients with SLE, although causality could not be further addressed by this study.

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