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Thrombosis and Lymphoma Stalk Lupus Patients

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Hydroxychloroquine Reduces Thrombosis in Systemic Lupus Patients

Patients with systemic lupus erythematosus (SLE) are at heightened risk of thrombosis [Mok CC et al. *Arthritis Rheum* 2005] and mortality [Cervera R et al. *Medicine (Baltimore)* 2003]. Additionally, women with SLE are also 2.05 to 2.27 times more likely to have a cerebral vascular accident (CVA)/myocardial infarction (MI) [Ward MM. *Arthritis Rheum* 1999 (Feb)].

Genevieve Law, MD, PhD, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, explained that thrombotic risk factors include demographic and cardiovascular traits, acquired thrombosis triggers, genetic hypercoagulable states, acquired lupus-specific risk factors, and persistent antiphospholipid antibodies. Prednisone is also a risk factor for thrombosis.

In the Study of the Predictors of the Course and Early Outcome of Patients with Systemic Lupus Erythematosus: Nature Versus Nurture [LUMINA] cohort, the highest dose of prednisone was associated with thrombosis [Burgos P et al. *Rheumatology* 2010]. Dr. Law said prednisone may be a proxy for disease activity. Conversely, hydroxychloroquine (HCQ) has antithrombotic effects [Rand JH et al. *Blood* 2008; Edwards MH et al. *Circulation* 1997].

In this study, objectives were to explore risk factors for incident thromboses in a large SLE cohort, and to examine the use of prednisone and HCQ as factors that predict or protect against thrombosis. Patients from the Hopkins Lupus cohort who had never had thrombosis were enrolled between 1987 and October 2011. They were reviewed for arterial and venous thrombotic events (VTE). Univariate and multivariate modeling were used to assess the data.

Of the study subjects (n=1795), 93.3% were female, 56% were Caucasian, and 37% were African American. The mean age was 37.0±12.5 years. In over 10,508 person-years of follow-up, 193 VTEs were observed: 106 arterial (50% CVA, 30% MI), 83 venous, and 4 both. The incident rate of thrombosis was 18.4/1000 person-years.

Table 1 shows the current and cumulative prednisone use and risk of thrombosis. The risk of VTEs was significantly lower among those who were currently taking HCQ, eg, 14.6% rate of events/1000 patient-years (rate ratio, 0.5; 95% CI, 0.4 to 0.7; p<0.0001) and likewise for >6 months of current use (13.8 rate of events/1000 patient-years; rate ratio, 0.5; 95% CI, 0.3 to 0.7; p<0.0003). Table 2 shows the multivariate model hazard ratios and p values.

Dr. Law concluded that current prednisone was a stronger predictor of thrombosis than cumulative prednisone; that current HCQ use decreased the risk of thrombosis, particularly in individuals with positive antiphospholipid antibodies; that nonsteroidal anti-inflammatory use (primarily naproxen) was associated with a lower thrombotic risk in univariate analysis; and that aspirin use was not protective, likely due to the bias of indication.

Independent Peer-Reviewed Highlights about the

American College of Rheumatology 76th Annual Scientific Meeting

Lymphoma Risk in Systemic Lupus

Data have shown that people with SLE have both a heightened risk of developing non-Hodgkin lymphoma (NHL) and of dying from it [Bernatsky S et al. *Arthritis Rheum* 2006].

Sasha Bernatsky, MD, PhD, McGill University, Montreal, Quebec, Canada, presented new data regarding the relative importance of drugs versus disease activity in mediating the increased risk of lymphoma in SLE patients. Along with Drs. Ann Clarke and Rosalind Ramsey-Goldman and colleagues from the Systemic Lupus International Clinics, Dr. Bernatsky previously demonstrated that risk of hematologic malignancies were substantially increased in SLE patients (standardized incident rate [SIR], 3.01; 95% CI, 2.47 to 3.62), particularly NHL (SIR, 4.36; 95% CI, 3.43 to 5.47) and leukemia (SIR, 1.76; 95% CI, 1.04 to 2.78) [Bernatsky S et al. *J Autoimmun* 2013. In press].

The recent case-cohort analyses were performed within the multisite SLE cohort (n=30) used to evaluate cancer risk. Adjusted hazard ratios for lymphoma were generated from multivariate models. Drugs assessed included cyclophosphamide, azathioprine, methotrexate, mycophenolate, antimalarials, and glucocorticoids. Medications were treated categorically (ever/never) and as cumulative doses.

In total, 75 (72 NHL; 3 Hodgkin lymphoma) and 4961 cancer-free controls were studied. Most lymphomas were of B-cell origin. As in the general population, lymphoma risk in SLE was higher in males versus females and increased with age. Lymphomas occurred a mean of 12.4 years (median 10.9) after SLE diagnosis.

Results from adjusted and unadjusted analyses failed to show a clear association of disease activity with lymphoma risk. Prof. Bernatsky and colleagues could not conclude that any one drug was an independent risk factor, although there was a trend to greater use of cyclophosphamide use in lymphoma cases than in controls. Correlation made it difficult to differentiate the effects of medications from disease activity. However, the authors suggest that the data offer some reassurance for SLE patients who take immunosuppressive drugs since most of the lymphomas in SLE did not seem to be caused by these medications. Even in SLE patients exposed to cyclophosphamide, the absolute risk of lymphoma was relatively low (about 1 case per 1000 person-years of follow-up).

Table 1. Current and Cumulative Prednisone Use and Risk of Thrombosis.

Subgroup	Thrombotic Events (#)	PYs of Follow-Up	Rate of Events/ 1000 PYs	Rate Ratios (95% CI)	p Value
Current prednisone					
None	52	4922	10.6	1.0 (Ref gp)	
1–9 mg QD	40	2439	16.4	1.6 (1.1–2.4)	0.025
10–19 mg QD	49	1429	34.3	3.3 (2.2–4.8)	<0.0001*
>20 mg QD	43	599	71.8	6.5 (4.3–9.8)	<0.0001*
Cumulative prednisone					
None	29	2214	13.1	1.0 (Ref gp)	
<1 year (10 mg QD)	37	1557	23.8	1.6 (1.0–2.6)	0.075
1–3 years (10 mg QD)	30	1583	19.0	1.8 (1.1–3.1)	0.026
3–10 years (10 mg QD)	45	1767	25.5	3.0 (1.8–5.2)	<0.0001*
>10 years (10 mg QD)	9	370	24.3	3.7 (1.5–9.4)	0.0056

*Remained significant for both arterial and venous thromboses. Ref gp=reference group; PY=patient-year.

Table 2. Multivariate Model Hazard Ratios and p Values.

Variable and Contrast	HR (95% CI)	p Value
Currently taking HCQ	0.6 (0.4–0.8)	0.0016
Currently taking aspirin	1.6 (1.1–2.4)	0.027
Prednisone Dose		
None	1.0 (Ref gp)	
1-9 mg QD	1.3 (0.8–2.2)	0.29
10-19 mg QD	2.5 (1.5–4.1)	0.0003
>20 mg QD	4.6 (2.6–8.1)	<0.0001

HCQ=hydroxychloroquine; Ref gp=reference group.