Risk factors for thrombotic events in patients with systemic lupus erythematosus from different ethnic groups

Evaluation of: Kaiser R, Cleveland CM, Criswell LA: Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large multi-ethnic cohort. *Ann. Rheum. Dis.* 68, 238–241 (2009). In this study Kaiser *et al.* examined the risk factors for the occurrence of thrombotic events in systemic lupus erythematosus patients for the University of California, San Francisco (CA, USA) genetics project. Smoking and disease severity (history of nephritis and immunomodulatory use) were found to be risk factors for the occurrence of thrombotic events whereas hydroxychloroquine use was found to be protective.

KEYWORDS: hydroxychloroquine ■ lupus ■ risk factors ■ thrombosis

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Kaiser *et al.* recently examined the risk factors for thrombotic events in a large multi-ethnic systemic lupus erythematosus (SLE) patient population [1]. This is of paramount importance given that thrombotic events occur with increased frequency and at a younger age in patients with SLE [2–4]. Several explanatory risk factors for thrombosis have been identified in these patients; they notably include the presence of antiphospholipid (aPL) antibodies, older age and disease severity, whereas smoking has been associated with vascular thrombotic events [2–5]. Studies have been hampered by the number of patients studied, the frequency with which aPL antibodies have been determined, and the assays used to measure them; furthermore, to date multi-ethnic studies have not included a sizable proportion of Asian Americans.

Methods

A total of 1930 SLE patients from the University of California, San Francisco (UCSF; CA, USA) Genetics Project were studied. These patients were recruited through a variety of sources including hospitals, clinics, support groups and referral centers from Northern California and throughout the USA; the diagnosis of SLE was validated by review of medical records using the ACR criteria. Variables examined were those available in the database including demographic (age, gender, ethnicity, smoking, education and income) and clinical (presence of nephritis, medication usage, aPL antibodies and thrombotic events). Thrombotic events included were deep vein thrombosis (DVT), pulmonary embolism, cerebrovascular accident, myocardial infarction, retinal vein thrombosis and miscarriages (three consecutive first trimester or ≥1 second trimester). These data were obtained, for the most part, by review of all available medical records and from the patients during the intake interview. The associations between covariates and the outcome of interest were examined by univariable and multivariable analyses; subgroup analyses (aPL positivity; venous vs arterial thrombotic events, socioeconomic variables) were also performed. Finally, propensity score analyses were done to adjust for confounding by indication to further assess the protective effect of hydroxychloroquine.

Results

Although nearly 60% of the patients were Caucasian, there were over 250 Hispanics, and over 200 Asian/Pacific Islanders and African–Americans. As expected the majority of the patients (91%) were women with a mean age at diagnosis of approximately 33 years and mean age of 42 years at study entry. The proportion of patients who had ever smoked was relatively high at 40%; 22% of the patients had had one thrombotic event, 6% two events and 2% three or more events.

The most common thrombotic events were miscarriages (25%) followed by DVT (20%) and cerebrovascular accident (17%) whereas 22% had thrombotic events not within the list provided in the methods section of Kaiser *et al.* [1]. aPL antibody positivity (either anticardiolipin antibodies [ACL] or lupus anticoagulant [LAC]) occurred in 27% of the patients. A total of 10% of the patients exhibited both, aPL positivity and thrombotic events. In multivariable analyses, variables significantly associated with one or more thrombotic

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events were smoking (odds ratio [OR]: 1.26; 95% CI: 1.07–1.82; p = 0.011), history of nephritis (OR: 1.35; 95% CI: 1.02–1.78; p = 0.036), use of immunomodulatory therapy (cyclophosphamide, azathioprine, methotrexate, cyclosporine, mycophenolate mofetil or chlorambucil) (OR: 1.40; 95% CI: 1.08–1.82; p = 0.0110), aPL antibody positivity (OR: 3.22; 95% CI: 2.49–4.16; $p < 10^{-9}$) and disease duration (per 5 years OR: 1.26; 95% CI: 1.17–1.35; $p = 0.027 \times 10^{-7}$). When the reference group was comprised of patients aged 40 years or older, younger ages were protective (OR: 0.52–0.72; 95% CI: 0.35 to 0.54–0.78 to 0.97). Trend analysis demonstrated significance for smoking, history of nephritis, immunomodulatory therapy, and aPL antibody positivity. Hydroxychloroquine demonstrated a protective effect (OR: 0.67; 95% CI: 0.50–0.90; p = 0.008), which remained significant after propensity score analysis was performed (OR: 0.62; $p = 4.91 \times 10^{-4}$), albeit the details of this analysis are not provided. Subgroup analyses indicated a protective effect for venous thrombosis in the African–Americans, for DVT in the Asian Americans and for pulmonary embolism and myocardial infarction in women.

Discussion

Several interesting findings are described in this study which represents a large multi-ethnic group of ACR-defined SLE patients with nearly 10 years of disease duration at study entry. First, the study confirms the deleterious role of both aPL positivity and smoking in the occurrence of these events. Likewise it confirms the role of disease duration, older age (by inference) and disease severity (as inferred by a history of nephritis and the use of immunomodulatory therapy) while a protective effect was demonstrated for hydroxychloroquine. While some protective effect was observed for some specific thrombotic events as a function of ethnicity (venous events in Asian Americans and DVT in African–Americans), no ethnic-specific risk factors, or difference on the rates of thrombotic events as a function of ethnic group were identified. Unfortunately, because of the data collection methods, measurements of disease activity, organ damage and precise information about medication usage was not available.

Perhaps the most important observation emanating from this study is the one regarding hydroxychloroquine. We and others have demonstrated that its use is associated with less damage accrual (overall and in specific domains of the damage index, particularly renal and integument) [6–8] and increased probability of survival [9,10]; the beneficial effects of hydroxychloroquine in terms of thrombosis had only been reported by Ruiz-Irastorsa *et al.* [11] but had not been replicated by others until the data from the study by Kaiser *et al.* [1] became available. As noted, however, the depth of the clinical data in this study is such that no inferences can be made about either the dose of hydroxychloroquine or the duration of treatment needed for this beneficial effect to be expressed. Nevertheless, when coupled with the earlier data from the Canadian Hydroxychloroquine Study Group [12] indicating that its discontinuation is likely to be followed by flares and the studies alluded to, the data suggest that this compound is overall beneficial in patients with SLE and should be continued indefinitely unless a clear contraindication supervenes. Furthermore, contrary to the prevailing notion among some obstetricians (and even some rheumatologists), hydroxychloroquine can be safely continued during pregnancy. In all cases adequate ophthalmologic follow up is needed.

Future perspective

This study, along with others, demonstrates the value of establishing large repositories of SLE patients with well-defined phenotypic features. When coupled with sera and DNA repositories, such clinical registries may prove invaluable in the assessment of risk factors for the different morbid events that occur in this most heterogeneous and complex disease. These

Executive summary

- The study by Kaiser *et al.* and the literature on the subject indicate that disease- and nondisease-related factors predispose/protect systemic lupus erythematosus patients to/from the occurrence of thrombotic events.
- Nondisease predisposing factors include older age and smoking.
- Disease predisposing factors include disease duration, disease severity (inferred from clinical and therapeutic data) and antiphospholipid antibody positivity.
- After adjusting for confounding by indication using propensity-score analysis, treatment with hydroxychloroquine was clearly protective of the occurrence of these events.
- Coupled with the data from the literature, the data from Kaiser *et al.* support the use of hydroxychloroquine in all lupus patients, unless a clear contraindication for its use exists.

efforts, however, are labor-intensive and somewhat expensive, which is just beginning to be appreciated by our funding agencies.

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