Prevalence of Acquired Activated Protein C Resistance and Anti-Protein C Antibodies in Systemic Lupus Erythematosus

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BACKGROUND

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterised by increased cardiovascular risk, with a 5-20 fold increased risk for venous thromboembolism (VTE) compared to the general population. Antiphospholipid antibodies (aPL) constitute a major risk factor for thrombosis in patients with SLE, who frequently also have antiphospholipid syndrome (APS). The protein C pathway has a key role in the regulation of haemostasis and inflammation and could be pivotal in the development of thrombosis in patients with SLE regardless of aPL. APS patients with VTE have been shown to have increased acquired resistance to protein C (APCr) associated with a high prevalence of anti-protein C antibodies (aPC). The role of aPC and APCr in patients with SLE, especially aPL negative (-), is less clear. The aim of this study is to determine the prevalence of aPC in association with APCr and thrombosis in aPL/APS- patients with SLE.

METHODS

Sixty-one consecutively attending patients with SLE, classified according to the revised ACR criteria, have so far been enrolled and subdivided as follow: thrombotic APS (APS; n=15), aPL positive (+) no thrombosis (aPL+/T-; n=17), aPL- with a history of thrombosis (aPL-/T+; n=8), aPL- without a history of thrombosis (aPL-/T-; n=21). Patients with heritable thrombophilia were excluded. aPC levels were determined by in-house ELISA. APCr was determined using thrombin generation (TG) and was measured as %inhibition of endogenous thrombin potential by

exogenous recombinant human activated protein C (rhAPC) or by Protac (specific protein C activator) for activation of endogenous protein C.

RESULTS

In this ongoing study, aPC were detected in 44% of patients (APS: 53.3%, aPL+/T-: 47%, aPL-/T-: 48%, aPL-/T+-: 25%; p=NS). aPL+ had higher aPC levels compared to aPL- patients (median (IQR) = 36.7 (24.7-51.8) vs 26.1 (17.3-37.6) U/mL, p=0.04). Positivity to aPC was significantly associated with resistance to both rhAPC (p=0.01) and activation of endogenous protein C (p<0.001). APCr prevalence was similar in aPL+ (54%) and aPL- (45%) patients. Resistance to rhAPC was associated with resistance to activation of protein C (p=0.02), but was less frequently detected (30% vs 48% of all cases), especially in aPL- patients (13.8% vs 43.8% in aPL+; p=0.01). In comparison, resistance to rhAPC was higher in aPL+ compared to aPL- (p=0.02). There were no correlations with demographics or disease activity (assessed by BILAG-2004 or SLEDAI-2K). APCr and aPC positivity were less frequent in patients with a history of rash or serositis (p=0.01 and p=0.02 respectively).

CONCLUSION

aPC levels and resistance to exogenous APC were higher in aPL+ than aPL- patients. aPC were also detectable in aPL- patients with SLE, and were associated with APCr *in vitro*. In aPL- patients resistance to activation of protein C was more frequent than resistance to exogenous APC, suggesting a possible defect in the activation of protein C. Predictive clinical-pathophysiological models based on aPC-profile and APCr assays might offer important tools for identification and management of patients with SLE at increased thrombotic risk independent of classical cardiovascular risk factors and aPL.