Background: Correct interpretation of lupus anticoagulant (LA) tests is crucial for diagnosis of antiphospholipid syndrome (APS). However, testing patients during vitamin K antagonist (VKA) or other anticoagulants remains a contentious issue and has been discouraged by official guidelines because of interpretational problems affecting the mixing test. Similarly, the clinical significance of weak LA, especially in the context of VKA, remains uncertain and certainly needs a more thorough evaluation. Autoantibodies that recognise a phosphatidylserine/prothrombin (PS/PT) complex have been reported to be associated with APS and may have diagnostic relevance in these settings.

Objectives: To evaluate the reproducibility of LA testing when performed in different centres and to assess the diagnostic performance of anti-PS/PT in different clinical settings of APS.

Methods: aPL testing was performed in a blind fashion in 4 centres. LA was tested as per the current criteria from the ISTH Subcommittee on LA-Phospholipid-dependent antibodies. Thirty-two patients were enrolled in this study, as follows: 13 patients with thrombotic APS treated with vitamin K antagonist; 5 patients thrombotic APS treated with DOAC; 14 patients with transfusion/low aPL titre. Anti-PS/PT IgG/IgM (aPS/PT, Inova Diagnostics) were tested by ELISA. We analysed the categorical agreement and degree of linear association, for LA and aPS/PT, respectively.

Results: Demographic, clinical and laboratory characteristics are summarised in Table 1. Categorical agreement for LA among the centres, as expressed by Cohen’s kappa coefficients, ranged between 0.61 and 0.80 (as substantial agreement). The correlation among quantitative results in the aPS/PT IgG was strong (7/12, 58% patients on VKA) in which LA results were discordant (as defined by lack of agreement in ≥2 laboratories) or inconclusive. Conversely, in those cases, we observed a good correlation for aPS/PT IgG testing (Cohen’s kappa coefficients=0.81–1, Spearman rho 0.86).

Conclusions: Despite the progress in the standardisation of aPL testing, we observed up to 35% of discrepant results for LA, especially in patients on VKA. Our findings showed that some discordances in the reliability of LA testing still exist. The introduction of aPS/PT antibodies in the diagnostic process of APS might represent a further diagnostic tool, especially when LA is not available or not reliable.

REFERENCE:

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THE NET-EFFECT OF COMBINING RITUXIMAB WITH BELIMUMAB IN SEVERE SYSTEMIC LUPUS ERYTHEMATOUSUS

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Background: In systemic lupus erythematosus (SLE) patients, excessive formation of neutrophil extracellular traps (NETs) is observed while their degradation is impaired. In vitro, immune complexes (ICx) trigger NET formation while NET-derived DNA is a postulated autoantigen for anti-nuclear autoantibodies (ANAs), found in SLE. Based on these self-perpetuating mechanisms in SLE, we hypothesised that interfering with ICx formation should regress NET formation and potentially ameliorate disease.

Objectives: Investigate the effect of Rituximab+Belimumab therapy on pathogenic autoantibodies in relation to NET formation in severe refractory SLE

Methods: A phase 2A, open-label, single arm proof-of-concept study was performed wherein 16 SLE patients with severe, refractory disease were treated with a combination of CD20-mediated B-cell depletion with rituximab and sustained inhibition of B-cell activating factor with belimumab. Besides safety, the study’s endpoints were chosen to address the concept of autoantibodies in relation to excessive NET formation.

Results: We demonstrated that SLE-derived immobilised IgG, but not soluble IgG, induced excessive NET formation, confirming ex vivo that ICx mediate excessive NET formation in SLE. We showed that therapeutic intervention with RTX+BLM led to specific reductions in ANAs and regression of excessive NET formation. RTX+BLM appeared to be safe and achieved clinically significant responses: low lupus disease activity state was achieved in 10 patients, renal responses in 11 patients and concomitant immunosuppressive medication was tapered in 14 out of 16 patients.

Conclusions: This study provides novel insights into clinical benefit of reducing excessive NET formation in SLE by therapeutic targeting ANA production with RTX+BLM. Altogether putting forward a new treatment concept that specifically ameliorates underlying SLE pathophysiology.

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RITUXIMAB THERAPY IN SLE: EARLY RETREATMENT IS ASSOCIATED WITH LOWER DISEASE ACTIVITY AND A REDUCTION IN CORTICOSTEROID USE


Background: The recently published UK guidelines for the management of SLE recommend biologic therapy for severe or refractory disease. The British Isles Lupus Assessment Group Biologics Register (BILAG-BR) has shown rituximab (RTX) to be safe, effective and corticosteroid (CS) sparing when used to treat refractory SLE. In 2013 NHS England published an interim clinical commissioning policy statement with criteria determining when RTX can be used to treat SLE.

Objectives: We evaluated our centre’s RTX retreatment strategy in patients with SLE and the consequent outcomes (disease activity and CS dose).

Methods: Records for the first 50 patients receiving RTX for refractory SLE who consented to join BILAG-BR from our centre between December 2013 and January 2016 were analysed (data cut off July 2016). Demographics, disease activity,[RL] LAG 2004/SLEDAI-2K), change in CS dose, retreatment schedules and adverse events were analysed.

Results: Median(IQR) age and disease duration were 42.8 (33–53) years and 9.5 (4–15.8) years respectively. Male: female ratio was 1:25. 80% were Caucasian, 6% Asian, 4% Caribbean and 10% other. All patients met SLICC/ACR classification criteria for SLE. The median(IQR) SLEDAI-2K scores and BILAG 2004 scores reduced from 6 (4–8) to 4 (0–6) (p=0.001) and 28 (10–24.5) to 9 (2–15.5) (p<0.001) respectively at 6 months. Complete response was achieved in 62.8% patients (defined as loss of all BILAG A and B scores to ≤1B score with no new A/B scores in other organ domains). 66% patients lost all A scores at 6 months. Median(IQR) daily CS dose reduced from 10 mg(20) to 5 mg(0.5–9.5) at 6 months (P<0.001) and was 5 mg (0–6.63) at last reported visit (median(IQR) 13 (12–19.5) months). 16 patients did not fully respond to baseline treatment but 11 responded to retreatment. Serious infections (requiring hospital admission) occurred in 6 patients (12%).

30/50 patients received their 1st course of RTX at BILAG-BR baseline visit. 23 met criteria for active disease (at least 1A or 2B), 6 were taking an unnecessarily high maintenance CS dose, and 1 was planning pregnancy. Median(IQR) CS dose in this group at baseline was 10 mg(1.5–20.5) and 25 mg(3–9) at 6 months. 70.6% demonstrated complete response at 6 months. 17 (57%) went on to have retreatment due to active disease, of which 11 (64.7%) had responded at 6 months post retreatment. Median(IQR) time to retreatment was 8 (6–12) months.

20/50 patients had received retreatment at predetermined intervals prior to their baseline BILAG-BR visit. Median(IQR) numbers of previous RTX courses were 3 (2–6). Median(IQR) CS dose was 8.75 mg(0–11.3) at baseline BILAG-BR visit and 5.5 mg(0–10) at 6 months. Median(IQR) time from baseline to retreatment was 6 (6–9.5) months. Median(IQR) sustained response was 18 (13.5–18) months.

Conclusions: Historically, our centre used time from 1st to treatment to flare as a guide to a patient’s future RTX retreatment schedule; patients were, on average, treated 2 months earlier than those treated under the current commissioning policy. Findings suggest that earlier retreatment led to sustained disease control and reduction of CS dose with no increase in adverse events. 11/16 incomplete responders responded following retreatment. Early retreatment may be associated with better outcomes for the patient and further research is needed in this area.

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