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Letters to the Editor

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Intrarenal arterial stiffness is increased in systemic sclerosis patients with anti–ribonucleic acid polymerase III antibodies

Rheumatology key message

- Intrarenal arterial stiffness is increased in SSc patients with anti-RNA polymerase III antibodies.

SIR, SSc is an autoimmune disease characterized by endothelial dysfunction and skin and internal organs fibrosis [1]. The subclinical renal impairment (50% of patients) is characterized by an increase of Doppler indices of intrarenal arterial stiffness [2–4]. Recent data demonstrate strong associations between anti-RNA polymerase III antibodies and scleroderma renal crisis (SRC). SRC and major vascular complications usually develop in the first years of the disease [2]. The aim of this study was to evaluate the Doppler indices of intrarenal arterial stiffness in SSc patients with anti-RNA polymerase III antibodies.

We enrolled 33 consecutive SSc patients [28 female and 5 male; mean age 48.4 years (S.D. 11.2)] fulfilling the ACR/EULAR criteria: 11 with anti-RNA polymerase antibodies (ARAs), 11 with anti-topoisomerase I antibodies (ATAs) and 11 with ACAs [5]. Patients with double positivity for antibodies were excluded. The mean disease duration was 8 years (S.D. 5.4). Sixteen patients had lcSSc and 18 had dcSSc.

Patients with SRC, obstructive and vascular kidney disease, abnormal urinary sediment, glomerulonephritis, elevated serum creatinine concentration, uncontrolled systemic hypertension, hyperlipidaemia, cardiac and hepatic failure, diabetes, cerebrovascular and peripheral vascular diseases, coagulopathy, smokers and pregnant or breastfeeding women were excluded.

All SSc patients underwent treatment with nifedipine (30 mg/day), 20 patients were receiving prostanoid therapy and 13 received Bosentan. Thirty healthy controls [25 female and 5 male, mean age 47 years (S.D. 11.5)] were enrolled. The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by the Sapienza ethics committee.

SSc patients and healthy controls underwent Doppler US after acclimation (15 min) in a temperature-controlled room [22°C (S.D. 0.4)]. Renal Doppler US was performed using a Toshiba Aplio Ultrasound System SSA-790 equipped with a convex 3.5 MHz probe as in our previous studies [3, 4]. Nailfold videocapillaroscopy was performed with a videocapillaroscope equipped with a 500× optical probe according to Cutolo *et al*. [6]. Analysis for ANAs was performed by indirect immunofluorescence using HEp-2 cells (Euroimmun, Lubeck, Germany). ATA and ARA concentrations were measured using QUANTA Lite Scl70 ELISA (Inova Diagnostics, San Diego, CA, USA). All the results were expressed as mean (S.D.) or median (range). Group comparisons were made by Student's unpaired two-tailed *t*-test or Kruskal–Wallis test. Pearson or Spearman correlation coefficients (*r*) were used as appropriate. The chi-square test or Fisher's exact test was used to compare categorical variables. *P*-values <0.05 were considered significant.

The pulsatile index (PI) [1.26 (0.15) *vs* 1.04 (0.16)], resistive index (RI) [0.66 (0.04) *vs* 0.50 (0.05)] and systolic:diastolic (S/D) ratio [3.04 (0.52) *vs* 2.07 (0.21)] were significantly higher ($P < 0.0001$) in SSc patients than in healthy controls. In SSc patients, no statistical correlations were observed between Doppler indices and age and subset of disease. Doppler indices were significantly higher in SSc patients with ARAs than in SSc patients with ACAs or ATAs. The PI was higher ($P < 0.05$) in SSc patients with ARAs [1.37 (1.12–1.75)] then in SSc patients with ATAs [1.21 (1.04–1.38)] and ACAs [1.22 (1.06–1.42)]. The RI was higher ($P < 0.01$) in SSc patients with ARAs [0.69 (0.64–0.80)] than SSc patients with ATAs [0.64 (0.61–0.67)] and ACAs [0.65 (0.60–0.69)]. The S/D ratio was higher ($P < 0.05$) in SSc patients with ARAs [3.32 (2.72–5.11)] then in SSc patients with ATAs [2.79 (2.52–3.29)] and ACAs [2.85 (2.43–3.41)]. No significant differences in Doppler indices were observed between SSc patients with ATAs and ACAs (Fig. 1).

Twelve patients had an early capillaroscopic pattern, 9 patients had an active pattern and 12 patients had a late pattern. The median values of PI, RI and S/D ratio in the three capillaroscopic groups were, respectively, 1.15 (1.04–1.29), 1.24 (1.09–1.42) and 1.36 (1.16–1.75); 0.64 (0.60–0.69), 0.64 (0.66–0.68) and 0.68 (0.64–0.80); and 2.77 (2.50–3.29), 3.01 (2.74–3.41) and 3.15 (2.43–5.11). The PI ($P < 0.01$), RI ($P < 0.01$) and S/D ratio ($P < 0.05$) significantly increased with the progression of capillaroscopic damage.

Fifteen SSc patients had a history of digital ulcers (DUs). The PI [1.26 (1.09–1.75) *vs* 1.19 (1.04–1.42), $P < 0.05$], RI [0.67 (0.65–0.80) *vs* 0.64 (0.60–0.69), $P < 0.001$] and S/D ratio [3.06 (2.43–5.11) *vs* 2.78 (2.50–3.41), $P < 0.01$] were significantly higher in SSC patients with a history of DUs than in SSc patients without a history of DUs.

Doppler indices of intrarenal arterial stiffness were higher in SSc patients than healthy controls and they significantly increased with the progression of digital microvascular damage. These Doppler indices showed a negative correlation with glomerular filtration rate and they are a reliable marker of new DU occurrence [3, 4]. For the first time, we demonstrated that in SSc patients

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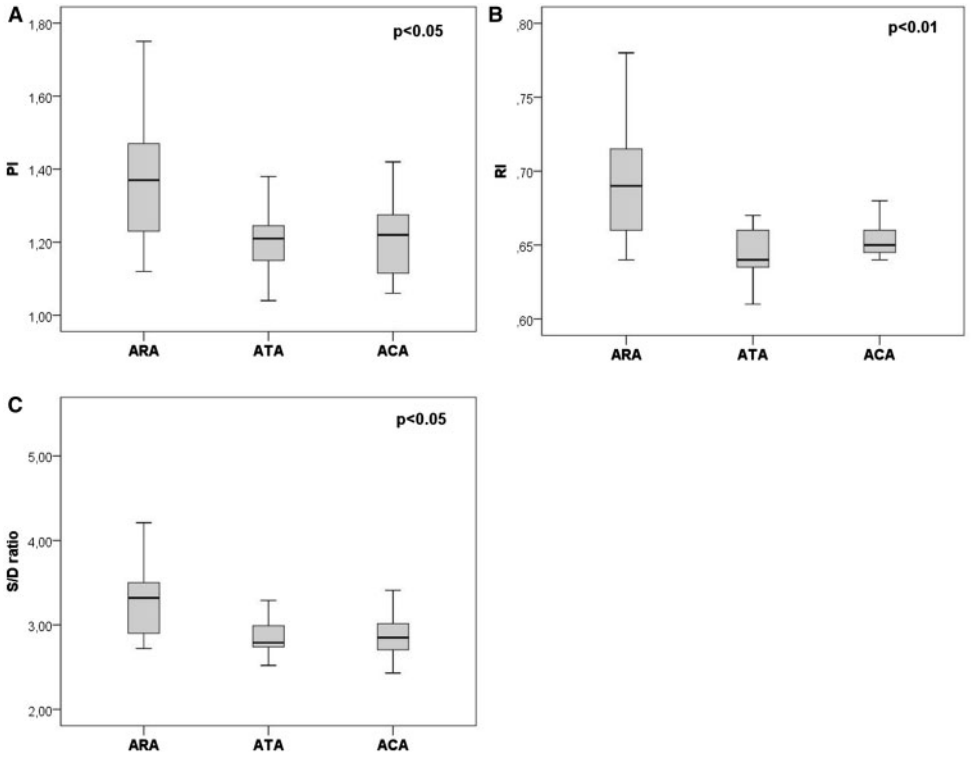
Fig. 1 Doppler indices in SSc patients



(**A**) Pulsatile index. (**B**) Resistive index. (**C**) Systolic:diastolic ratio. PI: pulsatile index; RI: resistive index; S/D: systolic:diastolic ratio; ARA: anti-RNA polymerase antibodies; ATA; anti-topoisomerase I antibodies.

with ARAs the Doppler indices of intrarenal arterial stiffness are higher than in SSc patients with ATAs and ACAs. Renal vasculopathy seems to be the main pathogenic mechanism of all SSc renal manifestations, including SRC. Although ARAs were immunologic predictors of developing SRC, we assume that they have a pathogenic role in subclinical renal vascular damage [7, 8].

We can hypothesize that in SSc patients with ARAs and elevated Doppler indices of intrarenal arterial stiffness there is a high risk of developing renal vascular complications.

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The potential overlapping populations for treatment with belimumab and rituximab using current NHS England and National Institute for Health and Care Excellence Guidelines in England and Wales

Rheumatology key message

- Of UK SLE patients with disease requiring biologic therapy, 13% are eligible for belimumab.

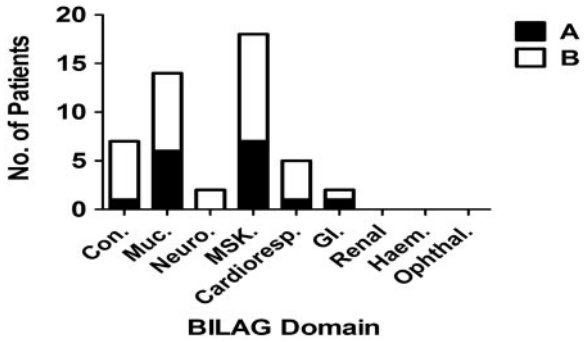
SIR, Belimumab, an anti-B lymphocyte stimulator mAb, has proven efficacy for the treatment of SLE [1, 2]. The European licence is based on *post hoc* analysis of randomized trials showing that predictors of better response include elevated antibodies to dsDNA, low complement and higher Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores [3, 4]. Patients with severe active LN or CNS lupus were excluded from these trials and do not form part of the patient population assessed as part of the marketing authorization [1, 2]. In June 2016, The National Institute for Health and Care Excellence recommended the use of belimumab as add-on therapy for patients with active auto-antibody-positive SLE, who have serological activity (defined as positive anti-dsDNA and low complement) and a SELENA-SLEDAI score $\geqslant 10$, despite standard treatment [5].

Since 2010, patients commencing biologic therapy for SLE in the UK have been registered in the BILAG-BR, the initial results of which are presented in a paper currently under review (McCarthy *et al.*, manuscript under review). We sought to investigate the number of patients and the clinical characteristics of patients treated with a biologic in the BILAG-BR who would potentially have been eligible for belimumab using this guidance [5].

Of the 270 patients registered for biologic use to November 2015, 82 (33%) had evidence of both low complement and elevated anti-dsDNA antibodies at enrolment. Of these, 46 (56.1%) patients had a BILAG A in the renal (n = 29) or neuropsychiatric system (n = 17), making them ineligible for therapy. An additional four (4.9%) had a SLEDAI score <10. Thus, from 2010 to 2015, 32 patients (13%) enrolled in the BILAG-BR would have been eligible for belimumab.

Amongst these 32 patients, the BILAG mucocutaneous (MUC) and musculoskeletal (MSK) systems had the most frequent A (MSK = 7, MUC = 6) and B scores (MSK = 11, MUC = 8; Fig. 1). Seventeen (53%) patients had a history of renal disease. The median [interquartile range (IQR)] baseline SLEDAI was 12.5 (12–15.75).

FIG. 1 BILAG-2004 organ systems with active disease in SLE patients eligible for belimumab



Number of individual patients scoring either an A or B on BILAG-2004 scoring system across the systems assessed.

Regarding medication use, 28 (87.5%) and 27 (84.4%) patients were on an anti-malarial or oral prednisolone, respectively. The median (IQR) baseline prednisolone dose was 15 mg (10–20 mg). The median (IQR) number of prior standard immunosupressant agents was 2 (1–3). MMF was the most frequently prescribed therapy (n = 23), followed by AZA (n = 15) and CYC (n = 11).

When we assessed response to Rituximab (RTX) in this cohort who would now be eligible for belimumab, the median (IQR) SLEDAI improved from 12.5 (12–15.75) at baseline to 4 (0–8) at 6 months ($P < 0.0001$). The total number of BILAG A scores reduced from 16 to 2 and B scores from 33 to 9. A corresponding reduction in CS dose was also noted from 15 mg (10–20 mg) to 6 mg (5–10 mg) at 6 months ($P < 0.001$).

Improved access to biologic therapies will enhance physicians' ability to control disease activity while facilitating CS tapering and preventing damage [6]. Given that the response rate to most biologic therapies in SLE is ~50%, the addition of belimumab to UK physicians' armamentarium is to be welcomed, especially for those patients who have not responded to conventional therapy. Our data will help inform clinicians and planners about the expected rates of usage and the clinical characteristics of patients requiring belimumab in the UK. MUC and MSK were the systems most likely to have active disease requiring belimumab. A history of renal involvement was, however, noted in ~50% of cases, emphasizing that previous renal involvement does not exclude patients from belimumab; indeed, both the Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS)-52 and 76 trials included patients with active renal disease, and a *post hoc* analysis suggested favourable renal outcomes in this population [7]. Our data also suggest that RTX remains a realistic therapeutic option for patients who fail to respond to belimumab.

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