Anti-C1q autoantibodies may not serve as an adequate biomarker for lung manifestations in systemic sclerosis: a single-centre, cross-sectional study

Dijkstra, D.J.; Liem, S.I.E.; Leeuwen, N.M. van; Fehres, C.M.; Vries-Bouwstra, J.K. de; Trouw, L.A.

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O.M. Moreno-Arrones,[1] D. Ortega-Quijano,[1] V. Perez-Brocal,[2,3] D. Fernandez-Nieto,[1] N. Jimenez,[1] E. delas Heras,[1] A. Moya[2,3,4] and B. Perez-Garcia[1]

[1]*Dermatology Department, Ramon y Cajal University Hospital, University of Alcala, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain;* [2]*Department of Genomics and Health, Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO-Public Health), València, Spain;* [3]*CIBER in Epidemiology and Public Health (CIBEResp), Madrid, Spain; and* [4]*Institute for Integrative Systems Biology (I2SysBio), The University of Valencia and The Spanish National Research Council (CSIC-UVEG), València, Spain*

Email: o.m.m.arrones@gmail.com

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Anti-C1q autoantibodies may not serve as an adequate biomarker for lung manifestations in systemic sclerosis: a single-centre, cross-sectional study

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Dear Editor, Systemic sclerosis (SSc) is a rheumatic disease characterized by fibrosis in the skin and internal organs, including the lungs, kidneys and gastrointestinal tract, as well as microvascular injuries.[1] Deaths related to SSc are mostly attributed to involvement of the lungs and the heart, with pulmonary fibrosis and pulmonary arterial hypertension (PAH) being the most common lung conditions associated with SSc.[2] Although the disease mechanism is not fully understood, it is clear that the pathogenesis of SSc involves a considerable immune component as evidenced by the presence of antinuclear autoantibodies (ANA) in the vast majority of patients.[3] ANA prominently target centromere proteins, topoisomerase and RNA polymerase III, and are often used as predictors of disease outcome and organ complications.[4] Recently, autoantibodies targeting complement component C1q were suggested to be predictive of pulmonary fibrosis or PAH.[5] As it would be highly desirable to have a biomarker for the most severe clinical presentation of SSc, we set out to replicate these findings in a Dutch cohort.

In this study, sera of 188 patients with SSc and 80 healthy controls were tested for the presence of anti-C1q autoantibodies. Patients were mostly female (149 of 188, 79%) and the median age was 56·6 years (interquartile range 46·8–65·5). Diffuse cutaneous SSc was present in 39 patients (21%). All patients fulfilled the American College of Rheumatology/European League Against Rheumatism 2013 SSc criteria, had a clinical diagnosis of SSc, and were included in the Combined Care in SSc cohort at Leiden University Medical Center.[6] Serum samples originated between 2012 and 2018. Presence of anti-C1q autoantibodies was determined in all sera by QUANTA Lite Anti-C1q ELISA (Inova Diagnostics, San Diego, CA, USA), using the cutoff for positivity of 20 units as recommended by the manufacturer.

In total, 21 (11%) patients with SSc and 10 (13%) healthy controls were assessed as positive for anti-C1q autoantibodies (Figure 1a). The prevalence of anti-C1q autoantibodies in healthy controls is not unexpected, as previous studies have reported frequencies between 2% and 13·5%.[7,8] We compared the occurrence of several clinical parameters, including interstitial lung disease (ILD) assessed with high-resolution computed tomography, ILD combined with a forced vital capacity (FVC) below 80% of predicted, and PAH, between anti-C1q-positive and anti-C1q-negative patients with SSc. PAH was defined as a mean pulmonary arterial pressure $\geq$ 25 mmHg at rest as assessed by right heart catheterization (RHC), including presence of precapillary pulmonary hypertension, defined by a pulmonary capillary wedge pressure $\leq$ 15 mmHg, and a pulmonary vascular resistance $>$ 3 Wood units on RHC. All patients with suspicion for PAH were referred for RHC. No significant differences were observed in the incidence of these SSc-related lung conditions between the patients who were anti-C1q positive or negative (Figure 1b).

Diffuse cutaneous disease was present in 33 of 167 (20%) anti-C1q-negative patients and in six of 21 (29%) anti-C1q-positive patients, a nonsignificant difference. Presence of anti-topoisomerase antibodies (ATA) and anti-centromere antibodies (ACA) was determined as part of diagnostics, with ATA often correlating with more severe disease. Interestingly, ATA were present at a higher rate in anti-C1q-positive patients (13 of 21, 62% vs. 32 of 167, 19% in anti-C1q negative patients;

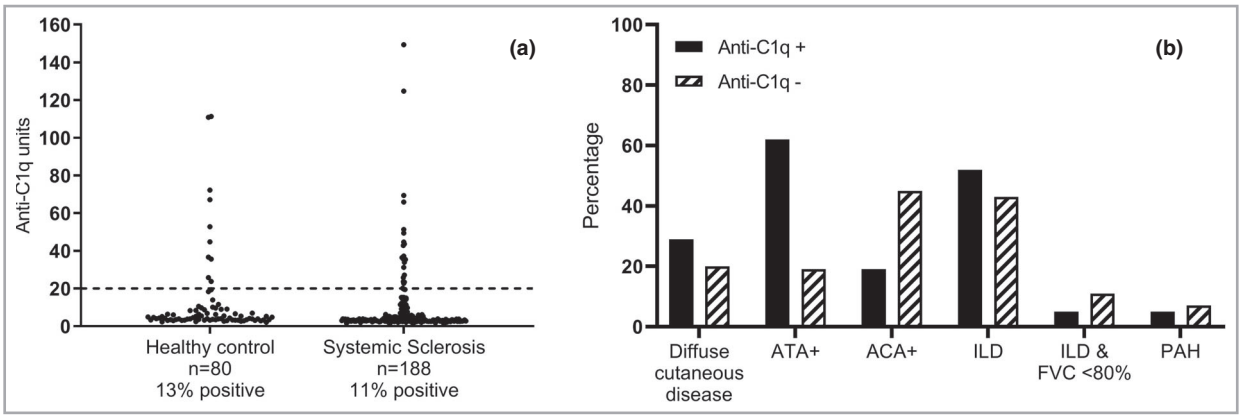

Figure 1 Anti-C1q in systemic sclerosis. (a) Anti-C1q autoantibodies in healthy controls and patients with systemic sclerosis, with the cutoff for positivity (20 units) indicated by the dotted line. (b) Percentage of diffuse cutaneous disease, presence of anti-topoisomerase antibodies (ATA) and anti-centromere antibodies (ACA), interstitial lung disease (ILD), clinically relevant ILD and pulmonary arterial hypertension (PAH) within anti-C1q-positive and anti-C1q-negative patients. FVC, forced vital capacity.

$P < 0{\cdot}001$), while there was no significant difference for ACA. Moreover, anti-C1q autoantibodies were found at a higher frequency in male than in female patients (nine of 39, 23% vs. 12 of 149, 8%; $P = 0{\cdot}008$).

The original study into anti-C1q autoantibodies in SSc found significantly more pulmonary fibrosis (55% vs. 28·8%) and more diffuse cutaneous SSc in anti-C1q-positive than anti-C1q-negative patients.[5] These findings suggested more severe disease in anti-C1q-positive patients. While in the present study ILD was found to be somewhat enriched in anti-C1q-positive patients (11 of 21, 52% in anti-C1q-positive patients vs. 71 of 167, 43% in anti-C1q-negative patients), this finding held no statistical significance. When investigating clinically relevant ILD (combined with FVC < 80%), the prevalence was even lower in anti-C1q-positive patients, and the same holds true for PAH. Furthermore, the observed association of anti-C1q with ATA, which is already reported to associate with lung complications, would detract from any added value of anti-C1q in SSc diagnostics. We therefore conclude that the presence of anti-C1q autoantibodies in our Dutch cohort is not correlated with SSc-related lung conditions. The aforementioned differences could be related to nonidentical patient populations in the respective studies. Compared with Liaskos *et al.*,[5] the current study includes a higher number of patients with SSc and a higher prevalence of ILD, but lower percentages of patients with diffuse cutaneous SSc and PAH. Nonetheless, the present study does not support a prognostic value for anti-C1q autoantibodies in SSc or its related lung conditions.

D.J. Dijkstra,[1] S.I.E. Liem,[2] N.M. vanLeeuwen,[2] C.M. Fehres,[2] J.K. de Vries-Bouwstra[2] and L.A. Trouw[1]

[1]*Department of Immunology Leiden and* [2]*Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands*

Correspondence: Leendert A. Trouw.

Email: L.A.Trouw@LUMC.nl

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Guidelines for the management of chronic spontaneous urticaria: recommendations supported by the Centre of Evidence of the French Society of Dermatology

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Dear Editor, Chronic spontaneous urticaria (CSU) is an inflammatory disease characterized by spontaneous weals or angio-oedema for more than 6 weeks. The natural history