Standardisation of the term "anti-Ro/SSA" in patients with Sjögren's disease and other disorders

Sirs,

Sjögren's disease (SjD) is a common B cell-driven chronic autoimmune disease with the hallmark features of sicca symptoms, fatigue and pain. Autoantibodies, such as those directed against the intracellular Ro/La ribonucleoprotein complex system, may be found in the majority of patients. In large international cohorts of SjD, anti-Ro/SSA may be found in up to 75% of patients, whilst those against La may be seen in up to 45% (1). Furthermore, as part of accepted classification SjD criteria, anti-Ro/SSA positivity is a qualifying criterion (2).

Historically, anti-Ro/SSA was first identified in the 1960s by immunoprecipitation assays in patients with systemic lupus erythematosus (SLE) (3). It was first termed anti-Ro [after the patient's serum in which the antibody was first recognised (4)] and then anti-Sjögren's syndrome antigen A (anti-SSA) when it was also identified in SjD patients. The antigenic targets were identified to be a 60 kDa protein involved in RNA quality control, and a 52 kDa protein (tripartite motif-containing protein 21 [TRIM21]) that functions as an E3 ubiquitin ligase and cytosolic Fc receptor (3). Despite the strong co-existence between autoantibodies to these two components, similar lines of gel immunoprecipitation and similar nuclear co-localisation, there is currently no evidence that the two autoantigens are molecularly linked nor do antibodies against one autoantigen cross-reacts with the other (5).

Rather ambiguously, a large number of scientific and clinical studies in SjD refer to their patients as either anti-SSA-positive or anti-SSA-negative without qualifying which serum IgG (anti-Ro52/SSA/TRIM21 and/or anti-Ro60) are present. As a case in point, the number of PubMed publications in the last 10 years (2015-2024) of different permutations of Ro/SSA + "Sjögren" were quantified, showing a vast predominance of publications that do not specify the exact autoantibody (Fig. 1).

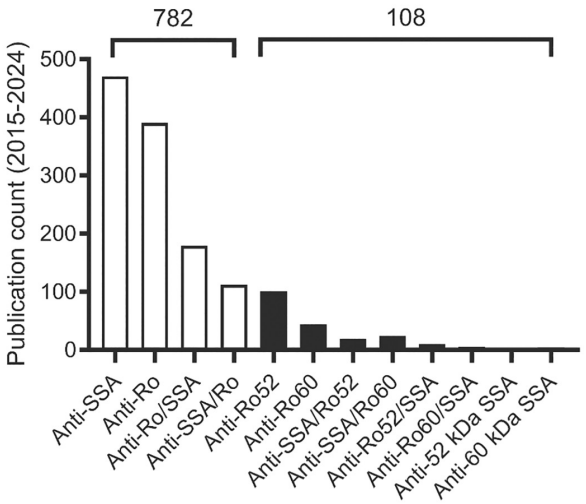

Fig. 1. Frequency of Sjögren's disease publications in the last 10 years (2015-2024) that use a specific combination of autoantibody terms.
Data derived from Pubmed.

This is not desirable as a number of studies are now emerging showing quite distinct clinical and laboratory characteristics of SjD with different combinations of anti-Ro52/TRIM21 and anti-Ro60 (6). Monopositive anti-Ro52/TRIM21 is seen in 6-7% of SjD patients, monopositive anti-Ro60 in 6-21%, and double positive to anti-Ro52/TRIM21/Ro60 in 53-67% (7). Patients with dual positivity to Ro52/TRIM21 and Ro60 tend to display greater prevalence of parotidomegaly, arthritis, hypergammaglobulinaemia and positive rheumatoid factor compared to SjD patients that were single positive to one of these autoantibodies or negative (7). Pathologically, these double-positive patients also had higher interferon signature scores, mirroring the increased pathological features seen in these patients (7). Thus accurate serological phenotyping may help with better prognostication and monitoring of SjD patients.

Using specific terminology could, arguably, be applied to other diseases as well. The predictive potential of each autoantibody was seen in SLE where monopositive anti-Ro52/TRIM21 patients were more likely to have renal insufficiency, whilst those with double positivity to Ro52 and Ro60, were more likely to have cytopenias (8). Furthermore, the combinations of autoantibodies may provide diagnostic clues when evaluating patients for autoimmunity. The presence of double positivity to anti-Ro52/TRIM21 and anti-Ro60 occurs more frequently in patients with SLE and SjD. Monopositivity to anti-Ro60 is more likely to be found in SLE than SjD and monopositive anti-Ro52/TRIM21 patients are less likely to have an immunological/autoimmune diagnosis (5, 8, 9). Neonatal lupus erythematosus occurs mostly in mothers who are anti-Ro52/TRIM21 and/or anti-Ro60 positive, particularly the former, with evidence that the autoantibodies may be directly pathogenic (10, 11). These examples highlight the importance of knowing the specific autoantibody rather than relying on the general anti-SSA/Ro term.

In brief, we argue that clinicians and laboratory personnel involved in autoimmune serology testing ought to be aware of the differences between anti-Ro52/TRIM21 and anti-Ro60. "Anti-Ro/SSA" by itself is somewhat ambiguous as it may refer to patients who have sera with IgG reactivity to Ro52/TRIM21, Ro60 or both. In the case of clinicians, it would be prudent to investigate if their local laboratory distinguishes between the two in the laboratory reports. Several formats of the autoantibody terminologies have been used to help clarify the specificity (Fig. 1). The author has used the popular "Ro52/TRIM21" and "Ro60" nomenclature throughout (Fig. 1); however, "Ro52" may be a medical misnomer since the original "Ro" serum (4) may not have had antibodies towards the 52 kDa autoantigen since this autoantigen does not reliably produce a precipitate on gel-based assays. Considering the push for harmonisation in immunology, the standardisation of "anti-Ro/SSA" nomenclature could be considered. Whatever format is used, it is important to be specific and clear with the terminology, for there are growing studies that highlight the clinical benefit of separate testing and reporting.

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