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Drs. Monsalve and Anaya reply

To the Editor:

We would like to thank Dr. Panchovska for her comments on our editorial[1], which was motivated by the work of Sharma, *et al*[2], who reported patients with sicca (100%) and other symptoms such as arthralgia (82%) and constitutional symptoms (43%) among others, in whom the presence of anti-Ro/SSA antibodies allowed a diagnosis of Sjögren syndrome (SS) despite a negative minor salivary gland (MSG) biopsy [i.e., focus score (FS) = 0].

The diagnosis of SS is based on the combination of symptoms (mainly sicca symptoms) and the presence of the autoimmune characteristics: activation of T cells (i.e., positive salivary gland biopsy) or B cells (i.e., presence of autoantibodies). However, not all the individuals presenting sicca symptoms have SS. No single test of oral or ocular involvement is sufficiently sensitive and specific to form a standard diagnosis of SS. Only the simultaneous positivity of various tests with the presence of subjective symptoms and serological abnormalities (anti-Ro/SSA and anti-La/SSB antibodies), and/or the presence of a score that is more than an FS on the MSG biopsy allow sufficient accuracy in the diagnosis of this disorder. In brief, a correct diagnosis is based on clinical suspicion, laboratory tests, and differential diagnosis.

In patients with negative MSG biopsy, the positivity of anti-Ro/SSA antibody is a key point based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria[3]. The sensitivity and specificity of these criteria reported in the original validation cohort was 96% (95% CI 92–98) and 95% (95% CI 92–97), respectively[3]. However, Tsuboi, *et al*[4] reported that the current ACR/EULAR criteria have significantly higher sensitivity (95.4%) and lower specificity (72.1%) in comparison with the other past criteria. These results were confirmed by van Nimwegen, *et al* in a Dutch cohort[5].

As mentioned by Dr. Panchovska[6], anti-Ro/SSA antibodies are found not only in patients with SS but also in patients with other autoimmune diseases, as well as in healthy individuals. Clinical and immunological associations are different depending on the presence of anti-Ro52 or anti-Ro60 antibodies and the assay used for their detection[7]. Anti-Ro52 together with anti-Ro60 positivity is more likely to be associated with SS[8]. Isolated anti-Ro52 antibodies lack of specificity and sensitivity for SS diagnosis, being of particular interest in the diagnosis of inflammatory myositis or systemic sclerosis[8,9]. Isolated anti-Ro60 antibodies, although rare, are mainly associated with systemic lupus erythematosus[8].

Although several genetics factors have been described to be associated to SS, including HLA alleles, so far they are not diagnostic tests[10]. Identification and evaluation of novel biomarkers will be useful to elucidate pathophysiology, classification of clinical subphenotypes, prediction of complications, and as diagnostic tools. For instance, antisalivary protein 1, anticarbonic anhydrase 6, and antiparotid secretory protein antibodies occur before anti-Ro/SSA or anti-La/SSB antibodies[11]. Sialic acid-binding immunoglobulin-like lectin 5 might be promising due to its association with severity of hyposalivation and ocular surface damage[12]. Alpha-enolase, cystatin S, and β2-microglobulin have been also suggested, but none of them have been clinically validated[13,14,15].

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