

Reply to the comment on: Clinical impact of anti-SSA antigenic specificity on disease activity and patient-reported outcomes in primary Sjögren's disease: a real-life cohort study

Dear Editor,

We sincerely thank the authors for their interest in our study and for their thoughtful comments regarding the clinical implications of anti-SSA antigenic specificity in primary Sjögren's disease (SjD) (1). Their observations provide an opportunity to further clarify the interpretation of our findings. First, we fully agree that comorbidities, particularly fibromyalgia, may significantly influence patient-reported outcomes such as ESSPRI. In our cohort, fibromyalgia was indeed more frequent among patients with isolated anti-Ro60 positivity, a finding that we explicitly reported and discussed as a potential contributor to the higher symptom burden observed in this subgroup. However, rather than representing a confounding factor, we suggest that this association may itself reflect a clinically relevant aspect of the anti-Ro60 subset. Increasing evidence indicates that systemic inflammatory activity and symptom burden often represent partially independent dimensions of disease expression in SjD. From this perspective, the enrichment of fibromyalgia and symptom-dominant presentations among anti-Ro60-positive patients may identify a clinically relevant subset that warrants recognition in routine practice.

Importantly, our findings are also consistent with previous studies showing that isolated anti-Ro60 positivity is associated with lower systemic inflammatory activity and fewer objective disease manifestations than other anti-SSA profiles. Deroo *et al.* reported that mono-anti-Ro60 patients exhibited the lowest frequency of glandular involvement and

biological markers of B-cell hyperactivity. Similarly, isolated anti-Ro60 positivity has repeatedly been associated with the milder end of the inflammatory disease spectrum (2). Second, we also agree that the triple-positive anti-Ro52/Ro60/La subset represents the biologically most active phenotype. Indeed, Bettacchioli *et al.* (3) demonstrated that anti-Ro52-containing profiles are associated with enhanced type I interferon activation, increased BAFF levels, B-cell hyperactivity, and more severe systemic disease manifestations. Our findings are consistent with this pattern, as both double-positive and triple-positive patients showed greater biological and systemic disease activity than patients with isolated anti-Ro specificities.

However, we do not believe that the lower ESSPRI scores observed in triple-positive patients contradict the concept of interferon-driven disease severity. Rather, this finding reflects the well-recognised dissociation between objective inflammatory burden and patient-reported symptoms in SjD. The relationships among immune activation, tissue damage, pain perception, fatigue, and illness experience are complex and not necessarily linear. Consequently, patients with the highest degree of biological and systemic disease activity do not invariably report the highest symptom burden.

Therefore, taken together, our observations suggest that anti-Ro52 and anti-Ro60 specificities may capture different aspects of disease heterogeneity. Specifically, our data indicate that anti-Ro52-containing profiles appear to be more closely linked to systemic immune activation and disease activity, whereas isolated anti-Ro60 positivity identifies patients with relatively limited inflammatory activity but substantial symptom burden. In this context, the apparent dissociation between ESSDAI and ESSPRI observed across serological subsets should not be regarded as contradictory, but rather as a reflection of the heterogeneity of SjD.

We thank Fang and Hou for their insightful comments, which further emphasise the importance of integrating serological profiling, objective disease activity and patient-reported outcomes when interpreting disease expression in SjD. We agree that future studies incorporating longitudinal assessments and biological characterisation will be instrumental in clarifying the mechanisms underlying these distinct clinical phenotypes and in determining how anti-SSA antigenic specificity may contribute to patient stratification and personalised disease management.

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on behalf of all authors

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Competing interests: C. Baldini has received consultancies from Amgen, Argenix, Aurina, Johnson & Johnson, Novartis and Vor Bio.

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References

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