Response to: 'Correspondence on 'Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial" by de Wolff *et al*

We read with interest the correspondence on our article 'Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial' by Wolff *et al*[1] in which the use of a composite endpoint, combining disease activity, functional and serological parameters, the newly developed CRESS[2] in future primary Sjögren's syndrome (pSS) trials is discussed, to lower placebo response and facilitate inclusions in clinical trials.

As suggested by Wolff *et al*, a composite endpoint including multiple important pSS features might reveal more appropriate than only Eular Sjögren Syndrome Disease Activity index (ESSDAI) or only gland function as primary endpoint in this complex and heterogeneous disease to lower placebo response. We agree this is an important point to consider for future trials. As mentioned in our reply[3] to the correspondence from Wang *et al*,[4] NECESSITY, a European initiative, will combine data from our trial[5] with those of previous randomised trials to determine new clinical composite outcomes in pSS, capturing both systemic and glandular features of the disease. An initiative from OMERACT on clinical outcomes in pSS is also ongoing on this crucial topic.

Wolff *et al* also suggest that another advantage of a composite endpoint might be to facilitate a broader inclusion of patients with pSS in clinical trials, that is, to allow the inclusion of patients with either an active systemic disease or a high burden of symptoms such as fatigue or dryness. However, in pSS, the pathogenesis of fatigue and dryness remains uncertain, with no key pathogenic cytokine or cell population identified to date. Targeting a unique goal to achieve a relevant improvement concomitantly in systemic activity, fatigue and dryness remain a great challenge in pSS. Indeed, even in the few recent positive phase II clinical trials, no drug was capable to improve all these three dimensions of the disease. Therefore, focusing on the evaluation of symptoms or systemic manifestations related to the pathway targeted might reveal more straightforward than a composite outcome. To increase the odds of finding effective drugs, biomarkers are also needed to stratify patients according to a molecular endotype amenable to a specific targeted therapy.

We therefore definitively hope that a relevant composite score will emerge from CRESS, NECESSITY and OMERACT initiatives and that the ongoing collective effort to clarify the pathogenesis of the disease will allow to make pSS enter the individualised medicine age.

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