Composite endpoints for Sjogren's Syndrome Authors' reply

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pneumonia, lymphadenopathy, and arthritis) rather than glandular involvement. Dryness should be managed with topical therapy as a first step, with systemic therapies used by patients with active disease. Systemic manifestations should be treated in an organ-targeted approach with subsequent therapeutic steps.[3,4] Although the clinical ESSDAI was included in the CRESS, thereby taking into account major organ involvement, in my opinion this feature was not given sufficient weight. As such, the CRESS scoring system might not be an optimal tool for evaluating disease activity in patients with Sjögren's syndrome.

We declare no competing interests.

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Authors' reply

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We thank Cristian Baicus and Derya Yildirim and colleagues for their interest in our Article[1] describing the novel outcome measure Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS).

We agree with Baicus that it is important to consider patient-reported outcome measures when evaluating treatment responses in patients with primary Sjögren's syndrome, but we believe it is best to combine these measures with other clinically relevant and more objective measurements. Past randomised controlled trials that used patient-reported outcome measures as the primary endpoint did not show beneficial treatment effects versus placebo, indicating that it is not optimal to use only subjective measures.[2] It is preferable to combine European League Against Rheumatism (EULAR) Sjögren's Syndrome disease activity index (ESSDAI) with EULAR Sjögren's Syndrome Patient Reported Index, which are complementary measures. Persistent systemic disease activity leads to chronicity of the disease (sometimes irreversibly), which should be prevented with effective treatment. Baicus also states that the ESSDAI is not patient oriented, but some domains of this measure are based on patient's information (eg, the constitutional domain). The objective dryness measurements are included because these measurements reflect glandular function, which is central to the disease process, and are complementary to subjective dryness measurements. This approach is supported by the fact that these measurements are included in the American College of Rheumatology and EULAR classification criteria. The author's statement that a patient does not care if the saliva volume increases by a few millilitres seems inconsiderate, as a small amount of saliva can make a lot of difference in patients who have little to no saliva. In patients with early disease, no further worsening of gland function might even be a treatment goal worthy to strive for. Nevertheless, we realise that not only the volume, but also the quality of the saliva is important. Previous research suggests that there is a weak association between subjective and objective dryness measurements, in which many factors seem to play a role, including patient's perception of their symptoms, and the composition of saliva and tears.[3]

Yildirim and colleagues suggest that systemic immunosuppressive treatment should be reserved for patients with organ involvement and, therefore, systemic disease activity should have a higher weight in the CRESS than it currently does. First, many randomised controlled trials did not meet their primary endpoints and showed large placebo effects when using ESSDAI as the primary endpoint.[4] Second, there is a high unmet need for effective therapy for all patients with primary Sjögren's syndrome. The notion that immunosuppressive therapy should only be supplied to patients with moderate to high systemic disease activity undermines the burden of dryness, fatigue, and pain experienced by these patients. Furthermore, Yildirim and colleagues question whether the serological item is appropriate for assessing response in rituximab-treated patients. The serological parameters included in the CRESS (rheumatoid factor and IgG) are important markers of disease activity in daily clinical practice. Therefore, a serological response is an indication that the drug is working—certainly when patients respond on two additional CRESS items, which is needed to achieve a CRESS response. Moreover, we used data from two rituximab trials on rheumatoid factor and IgG to determine appropriate cutoff points.

In summary, because primary Sjögren's syndrome is a heterogeneous disease, we believe treatment response should not be measured using only one aspect but rather should be based on multiple clinically relevant measurements. The CRESS combines five complementary, well-balanced items assessing systemic disease activity, patient-reported symptoms, tear and salivary gland function, and serology. The combination of the included CRESS items is widely supported in the Sjögren's community, including patient organisations, as illustrated by the confirmation of these outcomes as core set measures in the European Innovative Medicines Initiative project NECESSITY.[5]

We believe that, because of the combination of these measurements, CRESS will be an important tool in the search for new, effective therapies for primary Sjögren's syndrome.

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Antibody kinetics in patients with rheumatic diseases after SARS-CoV-2 mRNA vaccination

Persistence of antibody response after two-dose SARS-CoV-2 mRNA vaccination has been shown for up to 6 months in immunocompetent populations.[1] We previously confirmed a robust SARS-CoV-2 antibody response in most patients with rheumatic and musculoskeletal diseases; however, we found attenuated responses in patients on lymphocyte depleting agents.[2] Although antibody titres among organ transplant recipients 3 months after completion of an mRNA vaccine series were mostly stable,[3] the kinetics of antibody response in other immunosuppressed populations remain to be defined. Here, we present anti-spike antibody titres over a 3-month period in patients with rheumatic and musculoskeletal disease who completed the two-dose SARS-CoV-2 mRNA vaccine series.

We included patients with rheumatic and musculoskeletal disease on immunosuppressive medication who received two doses of mRNA (BNT162b2 [tozinameran] Pfizer–BioNTech or mRNA-1273 [elasomeran] Moderna) SARS-CoV-2 vaccine. Participants were recruited via social media postings by national rheumatic and musculoskeletal diseases organisations and advocacy groups, as well as through clinician referral. Baseline demographics and clinical characteristics were collected via electronic questionnaire. Participants with previous SARS-CoV-2 infection were excluded. Antibody testing was done 1 month and 3 months after dose 2 with the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay (EIA); range <0·4 to >250·0 U/mL [positive test result was ≥0·8 U/mL]), which tests for antibodies against the receptor binding domain (RBD) of the spike protein. Participants completed vaccination between Jan 4 and April 21, 2021. Low-positive antibody response was defined as anti-RBD pan Ig of 0·8–50 units per mL; high-positive antibody response was defined as anti-RBD pan immunoglobulin of more than 50 units per mL.[3] This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540), and patients provided electronic informed consent.

We assessed serial samples from 809 participants. 745 (92%) were female, with a median age of 49 years (IQR 39–59). Inflammatory arthritis (355 [44%] participants), overlap connective tissue disease (188 [23%]), and systemic lupus erythematosus (147 [18%]) were the most common rheumatic and musculoskeletal disease diagnoses. Hydroxychloroquine (322 [40%]) and methotrexate (209 [26%]) were the most frequently reported conventional disease modifying antirheumatic drugs, whereas tumour necrosis factor alpha (TNFα) inhibitor therapy was the most common biologic agent (173 [21%]; appendix pp 1–2).

See **Online** for appendix

744 (92%) of 809 participants had a positive anti-spike antibody response at a median of 29 days (IQR 28–32) after dose 2 and 753 (93%) had detectable anti-spike antibody responses at a median of 91 days (87–94) after dose 2. Titres remained stable in 724 (89%) participants between 1 month and 3 months after completion of the vaccination series (table). Titres decreased in 37 (5%) of 809 participants, whereas an increase in titres was observed in 88 (11%) participants.

Among 669 participants with high-positive titres at 1 month, 637 (95%) remained stable and 32 (5%) had a reduction in titres by 3 months. Among 75 participants with low-positive titres at 1 month, 37 (49%) remained stable, 33 (44%) had high-positive responses, and five (7%) had titres that dropped below the threshold of positivity. Among 65 participants with negative antibody response at 1 month, 50 (77%) remained negative, while de novo antibody responses were seen in 15 (23%) participants at 3 months (table). All 15 participants with de novo response reported use of antimetabolite therapy, including azathioprine or mycophenolate. This finding might suggest delayed response in patients on lymphodepleting therapy (appendix p 3). Supporting this observation, among patients with low-positive titres at 1 month and high-positive titres at 3 months, 27 (82%) of 33 were on antimetabolite therapy.

56 (7%) of 809 participants did not have detectable antibody response at 3 months; the most

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