

LETTERS

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Effective viral vector response to SARS-CoV-2 booster vaccination in a patient with rheumatoid arthritis after initial ineffective response to messenger RNA vaccine

To the Editor:

The COVID-19 pandemic has posed a unique challenge in the management of rheumatic diseases. Immunosuppressed patients are at an increased risk of developing severe COVID-19 and may not derive full protection from the vaccine (1–5). Thus, it is paramount that clinicians develop strategies to protect rheumatic disease patients from infection with SARS-CoV-2 and its variants.

In this letter, we describe the clinical response in a 74-year-old man with seropositive, erosive rheumatoid arthritis (RA) that was initially diagnosed in 1974. The patient is currently receiving 200 mg of hydroxychloroquine daily, 25 mg of etanercept weekly, and 20 mg of leflunomide daily. With this RA treatment regimen, low levels of disease activity have been maintained over the last 5 years.

The patient received 2 doses of the messenger RNA (mRNA) vaccine mRNA-1273 (Moderna) without interruption of his RA treatment, with the first dose administered January 18, 2021 and the second dose administered February 11, 2021. In mid-April, a semiquantitative analysis revealed a spike protein receptor-binding domain (RBD) antibody level of 53.9 units/ml (normal reference range 0–2,500), and the results of a SARS-CoV-2 anti-spike (S1/RBD) IgG test were negative. An assay designed to detect blocking of the interaction between the SARS-CoV-2 spike protein RBD and the human angiotensin-converting enzyme 2 (ACE-2) receptor demonstrated <10% blocking activity (6). The results of an interferon- γ -release assay detecting SARS-CoV-2-specific

T cells were also negative (7). The patient and his care team presumed that his suboptimal response to the vaccine was due to the immunosuppressive medications he was taking at the time of vaccination.

Based on his test results, the patient obtained an additional vaccine dose on his own accord. On June 6, 2021, he received 1 dose of the viral vector SARS-CoV-2 vaccine Ad26.COV2.S (Johnson & Johnson). No side effects developed. In late June, a repeat semiquantitative analysis revealed a spike protein RBD antibody level of 2,455.0 units/ml, and the results of an S1/RBD IgG test were positive. The ACE-2 blocking assay demonstrated 90–100% blocking activity (Figure 1). The results of the interferon- γ release assay remained negative, suggesting that T cell-mediated immunity was not achieved. A blunted T cell response to the SARS-CoV-2 vaccine has been demonstrated in patients receiving medications such as methotrexate or tacrolimus, but, to our knowledge, it has not been evaluated in patients treated with leflunomide (8,9).

In summary, we describe an immunosuppressed patient who experienced an ineffective immune response after 2 doses of an mRNA SARS-CoV-2 vaccine. The patient subsequently achieved a robust antibody response after a booster vaccination with the Johnson & Johnson SARS-CoV-2 vaccine, all while continuing treatment with RA medications. Current guidance put forth by the American College of Rheumatology (ACR) does not recommend obtaining antibody testing after vaccination, in part due to a lack of clinically meaningful cutoff values for available antibody tests (10). The US Food and Drug Administration revised the emergency use authorization on August 12, 2021 for the 2 available mRNA SARS-CoV-2 vaccines to permit a third dose for certain immunocompromised patients, and the ACR does support

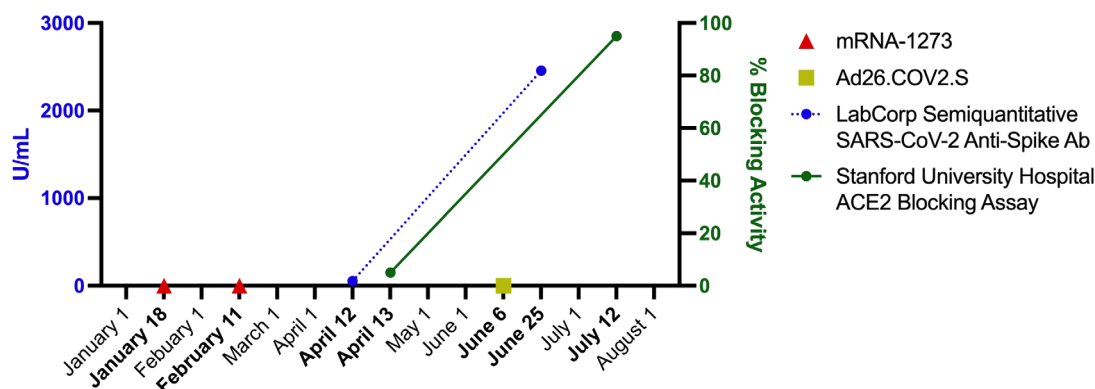



Figure 1. SARS-CoV-2 anti-spike IgG and human angiotensin-converting enzyme 2 (ACE-2) blocking activity before and after booster vaccination in an immunosuppressed patient with rheumatoid arthritis. Ab = antibody.

booster vaccination (11). Our report demonstrates the possibility of achieving humoral immunity against SARS-CoV-2 after initial failure through the use of a cross-platform booster vaccination strategy. Prior research has demonstrated that heterologous vaccination strategies may induce a more robust immune response in healthy adults (12–14). We believe future research is needed to establish relevant antibody reference values to identify patients without adequate protection against COVID-19 infection, and to understand the role of cross-platform booster vaccination when primary mRNA vaccination and/or booster vaccination fails to induce a sufficient immune response.

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Potential residual confounders in an analysis of lifestyle factors and risk of incident systemic lupus erythematosus: comment on the article by Choi et al

To the Editor:

We read with great interest the article by Dr. Choi and colleagues on whether a combination of individual factors related to lifestyle are associated with lower risk of incident systemic lupus erythematosus (SLE) (1). However, it is unfortunate that the analyses were not adjusted for residual confounders.

We have found that endometriosis, infection, and comorbidities are correlated with SLE, and could act as residual confounders in this type of an association analysis. For example, in a recently published study it was demonstrated that the risk of developing SLE is higher in patients with endometriosis compared to the general population, which shows an association between endometriosis and SLE (2). Therefore, the occurrence of endometriosis needs to be discussed when the majority of the participants in a study are female.

Furthermore, with regard to infections as a potential confounder, an association between *Helicobacter pylori* infection and a higher risk of SLE has been observed (3), and these types of triggers should be taken into account. Moreover, patients with SLE may experience several medical comorbidities. A recent study by Hansen et al demonstrated that multiple comorbidities are highly prevalent in SLE patients and can be identified both at the time of SLE diagnosis and up to 10 years before SLE diagnosis (4). Hypertension, chronic pulmonary disease, and depression were the comorbidities most commonly identified