Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pausing drugs and spacing vaccines: an open question

We read with interest the Article by Andrea Rubbert-Roth and colleagues,[1] which reported that among 53 patients with rheumatoid arthritis on various biological, conventional synthetic, and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), antibody responses to COVID-19 vaccination was reduced compared with healthy controls.

The authors reported that their data implied that successful vaccination of patients with rheumatoid arthritis who are taking DMARDs might depend on an interval of 3–6 weeks between vaccinations, but we propose that a longer interval might be of benefit to some patients. Methotrexate is known to reduce the immunogenicity of influenza and pneumococcal vaccinations,[2] and Haberman and colleagues suggested that this fact might also be true of COVID-19 vaccination in patients with immune-mediated inflammatory diseases.[3]

It is possible that a short discontinuation of methotrexate might increase the immune response that is induced by COVID-19 vaccination. Indeed, one study of seasonal influenza vaccination in patients with rheumatoid arthritis receiving methotrexate noted that, in people with stable disease (mean Disease Activity Score 28-CRP=2·3 [SD 1·1]), a discontinuation of the drug for 2 weeks after vaccination resulted in greater humoral responses, without a convincing increase in flares (5·1% *vs* 10·6%; p=0·070) or use of rescue medications (4·5% *vs* 6·3%; p=0·49).[4]

For an interval of 3 weeks between vaccine doses, methotrexate would need to be withheld for a total of 5 weeks. An interval of 12 weeks between doses of COVID-19 vaccine (ie, the recommended maximum interval in the UK)[5] would allow methotrexate to be safely discontinued for 2 weeks after to first dose, resumed for 10 weeks, and discontinued for a further 2 weeks after the second dose before returning to usual therapy. Another option would be the use of a single-dose vaccine, such as the Ad26.COV2.S vaccine (Janssen), which would require a pause in methotrexate therapy for just 2 weeks. In stable patients, this pause might allow optimisation of a vaccine-induced immune response without significant risk of disease flare. The external validity of these data is poor, and further research is required, particularly in patients with organ-threatening diseases (eg, antineutrophil cytoplasmic antibody-associated vasculitis and systemic lupus erythematosus). While we await large studies to support these findings, we suggest temporary methotrexate discontinuation as a pragmatic approach to maximising vaccine effectiveness in patients with a low risk of flare.

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Authors' reply

We thank Mia Rodziewicz and colleagues for their interest in our Comment[1] on the immunogenicity of mRNA-based vaccines against SARS-CoV-2 in patients with rheumatoid arthritis and their discussion regarding the interval between the two vaccine doses. Most of our patients (44 [83%] of 53) received the mRNA-based BNT162b2 (Pfizer–BioNTech) vaccine and nine (17%) patients received the mRNA-1273 vaccine (Moderna); the interval between the first and second dose was 3–6 weeks according to Swiss federal regulations, which were based on the intervals that were proposed by the manufacturers.

In contrast to mRNA-based vaccines, the ChAdOx1 nCoV-19 vaccine (AstraZeneca), which is used in the UK, consists of the replication-deficient simian adenovirus vector ChAdOx1 and the full-length structural surface glycoprotein (ie, spike protein) of SARS-CoV-2. To achieve a protective anti-SARS-CoV-2 immune response, two vaccine doses are considered to be necessary. In the case of a vector-based vaccine, concern exists regarding the use of an early homologous boost, because an anti-vector-directed immune response might interfere with the effectiveness of the second vaccine dose to induce a potent anti-SARS-CoV-2-directed