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# Discontinuing methotrexate to enhance vaccine response

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In patients with autoimmune rheumatic disease, methotrexate therapy has been associated with poor immune response to vaccines, including those intended to provide protection against COVID-19. Emerging evidence supports the practice of temporarily discontinuing this treatment in order to improve immunogenicity.

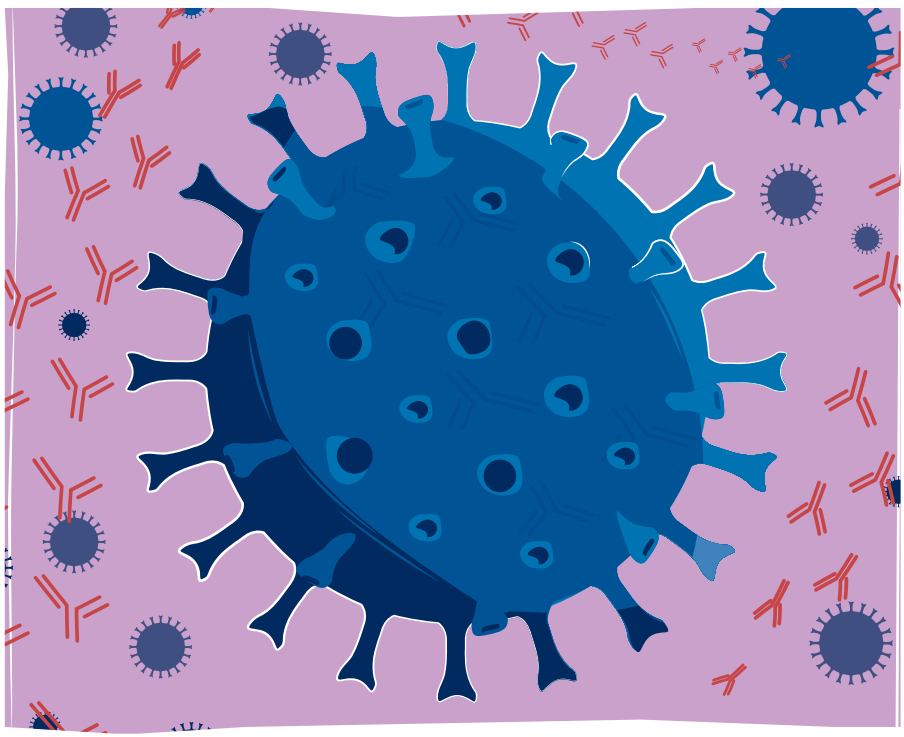
*Refers to* Arumahandi de Silva, A. N. et al. Pausing methotrexate improves immunogenicity of COVID-19 vaccination in elderly patients with rheumatic diseases. *Ann. Rheum. Dis.* **81**, 881–888 (2022).

Methotrexate is the anchor therapy for inflammatory joint symptoms in many diseases, especially rheumatoid arthritis (RA). It is widely used both as monotherapy and in combination with other agents, owing to its efficacy and adequate safety profile. However, methotrexate has been associated with poor humoral immune responses to many different vaccines, including those against SARS-CoV-2, in patients with autoimmune rheumatic diseases[1,2]. The short half-life of methotrexate and the rapid turnover of naive lymphocyte lineages provide a rationale for temporary discontinuation of this therapy near the time of vaccination as a strategy to enhance immunogenicity. In this context, Arumahandi de Silva et al.[3] retrospectively evaluated the value of this approach for patients receiving mRNA and viral-vector vaccines, and corroborated findings previously reported for influenza vaccines[4–6] and inactivated SARS-CoV-2 virus vaccines[7]. In fact, robust antibody responses are generally induced in a short period (~14 days) after each vaccine dose[3]. The responses can be even faster and stronger with a history of SARS-CoV-2 infection[2].

Evidence from a series of trials of influenza vaccination by Park et al.[4,5] demonstrated that withdrawal of methotrexate for 2 weeks after a single dose of seasonal tetravalent vaccine was associated with enhanced humoral response in patients with RA, without worsening disease activity. However, the challenging scenario for COVID-19 vaccination includes the option of several different vaccines, most of which have a two-dose schedule, with an interval between doses that can vary from 2–4 weeks to 12 weeks. The first version of the ACR guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases suggested a 1-week discontinuation of methotrexate after each dose of mRNA vaccine and a 2-week discontinuation period after the single-dose viral-vector vaccine for those with well-controlled disease[8]; by contrast, EULAR did not recommend any specific methotrexate-discontinuation strategy. In the German cohort studied by Arumahandi de Silva et al.[3], methotrexate intake schedules around vaccinations were heterogeneous: 33 patients had maintained methotrexate therapy, and 31 had changed their intake in one of several different patterns, including withdrawal before and/or after vaccination.

> “methotrexate has been associated with poor humoral immune responses to many different vaccines”

This retrospective analysis[3] revealed that methotrexate withdrawal for at least 10 days after the first and/or second dose, but not before, improved the humoral response to vaccination, regardless of the type of vaccine used. This finding is similar to that reported by Park et al. for influenza vaccination[4–6], which demonstrated that the timing of methotrexate interruption is crucial, with discontinuation of methotrexate before vaccination providing no improvement in immunogenicity, even with a pause of 4 weeks[5]; notably, the



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timing of the last dose of methotrexate before vaccination did not affect vaccine response[6].

Arumahandi de Silva et al.[3] found that patients who discontinued methotrexate had higher titres of IgG antibodies against receptor binding domain (RBD) proteins, higher vaccine response rates as defined by positive levels of RBD IgG and of SARS-CoV-2-neutralizing antibodies and higher virus-neutralizing capacity, in comparison with those who continued methotrexate therapy[3]. Both seropositivity for anti-RBD IgG and higher titres of SARS-CoV-2-neutralizing antibodies have been associated with increased protection against COVID-19 in patients with autoimmune rheumatic diseases[9]. The ~33% increase in the frequency of vaccine response according to anti-RDB IgG positivity seen in the methotrexate discontinuation group was even greater than the reported 12–34% improvement in response to influenza vaccine[4,5] and to the ~24% increase in IgG response to the inactivated anti-SARS-CoV-2 vaccine[7]. A ~21% higher response rate was also seen with methotrexate withdrawal when neutralization response was measured using a test that directly evaluates inhibition of RBD linkage. This finding contrasts with the modest and non-significant 13% improvement in response observed with the same strategy in patients receiving the inactivated SARS-CoV-2 vaccine[7]. The fact that mRNA vaccines were used in >85% of patients in the analysis by Arumahandi de Silva et al. probably accounts for this difference, since mRNA vaccines induce very specific anti-RDB antibodies at higher titres[3].

> “methotrexate withdrawal for at least 10 days … improved the humoral response to vaccination”

Age is well known to decrease vaccine immunogenicity, and this factor independently influenced vaccine response in all methotrexate-withdrawal trials, including the study by Arumahandi de Silva et al.[3]. Of note, in this study the benefit of pausing methotrexate was limited to elderly patients (≥60 years old); however, the patients aged younger than 60 years, who were underrepresented in the cohort, all responded very well to vaccination, precluding a definitive conclusion about the benefit of the methotrexate-holding strategy in the general adult population receiving COVID-19 vaccines. The results of the largest influenza vaccination study by Park et al., however, support the notion of an overall, age-nonspecific benefit of a methotrexate-holding strategy, as the mean age in the patient groups was approximately 53 years[4].

Although the use of DMARD combination therapy and glucocorticoids has also been associated with decreased response rates in larger COVID vaccine trials[2], their use did not seem to hamper the beneficial effect of discontinuing methotrexate in the analysis by Arumahandi de Silva et al.[3] and by Araujo et al.[7]. Regarding the use of glucocorticoids, methotrexate-holding studies[3–5,7] have solely included patients receiving no or low doses of prednisolone, and in the cohort analysed by Arumahandi de Silva et al. ~80% of patients were not being treated with glucocorticoids[3]. The benefit of methotrexate withdrawal has also been observed regardless of methotrexate being used as monotherapy or in combination with other drugs. However, the biologic DMARDs that interfere profoundly with humoral vaccine response, rituximab and abatacept, were not represented in the study by Arumahandi de Silva et al.[3] and were underrepresented in the other trials[4,5,7].

Regarding methotrexate dose, Park et al.[4] suggested that methotrexate has a dose-dependent detrimental effect on the immune response to influenza vaccine, with the benefit of temporary interruption being apparent in patients receiving doses greater than 10 mg per week. The analysis by Arumahandi de Silva et al.[3] included patients receiving methotrexate with mean doses similar to those in the trials by Park et al. (approximately 13 mg per week), whereas patients in the study of inactivated SARS-CoV-2 vaccine[7] were receiving a slightly greater median dose (20 mg per week) and no patients received a dose lower than 10 mg per week. In both anti-SARS-CoV-2 vaccine papers[3,7], methotrexate doses were comparable between the maintenance and withdrawal groups, and the dose did not impact the effect of methotrexate withdrawal.

Although Arumahandi de Silva et al.[3] did not study the safety of the methotrexate withdrawal strategy or its influence on disease activity, the results of influenza vaccination studies suggested that a 2-week withdrawal period does not affect control of RA disease activity[4,5], whereas in the trial of inactivated SARS-CoV-2 vaccine the frequency of RA flares increased after the second period of methotrexate withdrawal[7], probably owing to the short-term interval between the vaccine doses and therefore the withdrawal periods. This finding is consistent with data on the pharmacokinetics of methotrexate in patients with RA, in whom a 3-week discontinuation of methotrexate would be required for concentrations of its metabolites in red blood cells to fall below the therapeutic threshold, and with the fact that RA disease flares frequently occur approximately 1 month after stopping methotrexate[10].

Overall, the results of the retrospective analysis by Arumahandi de Silva et al. are consistent with those from other trials and support the strategy of discontinuing methotrexate for 10–14 days after each dose of COVID-19 vaccine in patients with well-controlled and stable autoimmune rheumatic disease. This strategy, however, requires close surveillance of disease activity and shared decision-making.

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**Competing interests**
The authors declare no competing interests.