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Withholding methotrexate after COVID-19 vaccination: different strategies, same results?

We read with great interest the Article by Teny Grace Skaria and colleagues[1] about the strategy of withdrawing methotrexate after the ChAdOx1 nCov-19 (Oxford–AstraZeneca) vaccine in patients with rheumatoid arthritis and psoriatic arthritis. Their study confirmed the benefit of 2-week methotrexate interruption after vaccination in a population of patients predominantly younger than 60 years (MIVAC I and MIVAC II), and further demonstrated the benefit of methotrexate interruption only after the second vaccine dose (MIVAC II)—a strategy that might lead to a lower incidence of flares.[1] Levels of antibodies against the spike receptor binding domain (anti-RBD) were comparable at the end of MIVAC I and MIVAC II, suggesting that withdrawing methotrexate after the second vaccine might be equivalent to withdrawing it after both vaccine doses. However, structural differences between the studies might preclude a definitive conclusion about the equivalence of the strategies regarding immunogenicity. MIVAC I excluded patients who were positive for anti-RBD or anti-nucleocapsid antibodies before the first vaccine dose; whereas MIVAC II only excluded patients with anti-nucleocapsid antibodies detectable after the first dose. This distinct baseline criterion most likely resulted in a greater number of patients with previous SARS-CoV-2 infection (ie, anti-RBD antibody positive or formerly anti-nucleocapsid antibody-positive patients who became negative before enrolment) in MIVAC II. Patients with previous SARS-CoV-2 infection are known to respond better to vaccines compared with patients who are naive to SARS-CoV-2.[2,3] In addition, studies have shown that post-infection longevity for anti-nucleocapsid antibodies was lower than anti-RBD antibodies and waned rapidly in immunosuppressed patients.[4,5] Therefore, MIVAC II might have included some patients with previous SARS-CoV-2 infection at baseline who were prone to a more robust vaccine response. Supporting this notion, a comparison (using χ^2 test) of overall MIVAC I and II patients' seroconversion rates after the first dose, as depicted in table 2,[1] showed that pooled MIVAC I patients had lower seroconversion rates (n=104 [66%]) than did pooled MIVAC II patients (n=126 [80%]; p=0·0039), regardless of the methotrexate holding strategy. Even among patients in methotrexate-hold groups, those who withdrew methotrexate after the first dose had lower seroconversion rates (MIVAC I n=50 [63%]) than patients who did not (MIVAC II n=63 [83%]; p=0·0044). In summary, MIVAC I and II populations are probably different regarding previous exposure to SARS-CoV-2, which might account for the comparable immunogenicity observed with different methotrexate discontinuation schemes. Stopping methotrexate solely after the second vaccine dose instead of after both doses in the primary vaccine schedule might be safer, but further studies are necessary to compare the immune benefit of these strategies.

We declare no competing interests.

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Author's reply

We thank Ana De Medeiros-Ribeiro and colleagues for their interest in our study. Before inclusion in the MIVAC-I study, patients were screened for anti-receptor binding domain (RBD) antibodies. Such screening was not done before MIVAC II because patients had already received one dose of the AZD1222 vaccine and were anti-RBD antibody-positive.[1]

De Medeiros-Ribeiro and colleagues suggest that this absence of screening for anti-RBD antibodies would lead to inclusion of more patients in MIVAC II with possible hybrid immunity who would have shown increased immunogenicity post vaccination. However, we have taken all other possible measures to exclude patients with past SARS-CoV-2 infection, including exclusion of known COVID-19 and nasopharyngeal RT-PCR-positive cases, individuals with symptoms of COVID-19 or acute febrile illness 6 months before random assignment, and primary contacts of SARS-CoV-2-positive cases, as well as screening for anti-nucleocapsid antibodies. Thus, it is theoretically correct that there might be individuals who have hybrid immunity in MIVAC II, but on a practical level, this number should have been mitigated by such stringent screening. Another reason patients are unlikely to have hybrid immunity is the relatively low antibody titres after the first dose of vaccine in all patients in the MIVAC trials. We had shown

previously that patients with previous SARS-CoV-2 infection develop very high antibody titres (>5000 IU/mL) after a single dose of vaccine; we found this to be the case even in patients on immunosuppression.[2] We have re-examined our data and identified 13 individuals who had antibody titres above 500 IU/mL, who were equally distributed between the two trials (six from MIVAC I, and seven from MIVAC II; p=0·6). The level of antibodies after the second dose in the methotrexate continuation groups of MIVAC I and II were similar. If there were significant number of people with previous SARS-CoV-2 infection in MIVAC II, this would have been expected to lead to higher levels of antibodies in the methotrexate continuation group of MIVAC II when compared with the same in MIVAC I.

De Medeiros-Ribeiro and colleagues have correctly pointed out that patients in MIVAC I who withheld methotrexate had lower seroconversion after the first dose than did any of the groups in MIVAC II (who continued methotrexate during the first dose). Although we do not have any specific hypothesis to explain why this effect occurred, serological response after only one dose of vaccine is variable in itself.[3,4] We agree with De Medeiros-Ribeiro and colleagues that further studies are needed to corroborate our findings.

Author declarations remain the same as in the original Article.

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