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Title: Withholding Methotrexate after Vaccination with ChAdOx1 nCov19 in Patients with Inflammatory Arthritis Two Parallel Randomized Controlled Trials (MIVAC I and II)

### **Editorial Title - Suspending methotrexate for 2-weeks after COVID-19 vaccination**

Dr Laura C Coates, PhD. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, UK

Professor Abhishek Abhishek, PhD. Academic Rheumatology, University of Nottingham, Nottingham, UK

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People with inflammatory arthritis treated with immune-suppressing drugs are members of a large, clinically vulnerable patient group that is at increased risk of hospitalisation and death from COVID-19 [1]. Effective vaccination against COVID-19 has improved outcomes worldwide but there have been concerns about their effectiveness in the immunosuppressed due to lowered COVID-19 vaccine induced immunity [2].

This study by Skaria and colleagues, reported the results of two clinical trials MIVAC I and II studying the impact of two week hold in methotrexate treatment on COVID-19 vaccine immunogenicity assessed using a binding antibody against the spike antigen in receptor binding domain (S1-RBD) [3]. The study showed that withholding methotrexate after each of the two doses, and after only the second dose of the ChAdOx1 vaccine both led to approximately two-fold higher S1-RBD antibody titres four weeks after the second vaccine dose compared to methotrexate continuation. Withholding methotrexate only after the second vaccine dose rather than both doses appeared to be non-inferior without an increased risk for arthritis flares. The positive impact of a temporary hold in methotrexate on vaccine induced immunity has been demonstrated with three different COVID-19 vaccine technologies [4, 5] and the influenza vaccine [6, 7]. These studies were relatively small, with short follow-up periods, and not designed to assess the effect of withholding methotrexate on risk of infections or their complications. Nevertheless, the consistency of effect across different vaccines makes the findings relevant to patient care and ought to be considered when planning future vaccinations against COVID-19 or influenza in this population.

In the MIVAC I and II studies, patients with prior COVID-19 were excluded from randomisation and analysis to provide a homogeneous population to test the effect of intervention on S1-RBD antibody levels. This is different from a previous study that included all patients regardless of prior COVID-19 infection status to provide more real-world evidence [4]. The two MIVAC trials addressed slightly different interventions but are complementary. The population in these studies was heterogeneous but reflective of the clinic population with well-controlled RA (>90% patients) and psoriatic arthritis with low disease activity. Appreciable proportion of patients were taking immune-suppressing disease-modifying anti-rheumatic drugs (DMARDs) with approximately 10%, 3% and 1% prescribed leflunomide, tofacitinib, and anti-TNF-alpha respectively. This raises the potential for future exploratory subgroup analysis to evaluate the impact of temporary suspension in methotrexate treatment on COVID-19 vaccine induced immunity in the context of additional immunosuppression.

The absence of an incremental effect on vaccine induced immunity from holding methotrexate after the first ChAdOx1 vaccine dose is intriguing. This may be due to relatively low serological immunogenicity of the first vaccine dose in this population – in the context of low immunogenicity, holding methotrexate for two-weeks post-vaccination might not have had a detectable immune-boosting effect. This finding may not hold true in the context of other vaccine technologies e.g. mRNA. Nevertheless, patients unvaccinated against COVID-19 or those who have received one dose of ChAdOx1 vaccine, and are intending to complete their primary vaccination using ChAdOx1 vaccine ought to only consider skipping methotrexate for two-weeks after the second vaccine dose.

Beyond this study, there are still unanswered questions. There have not been any detailed T-cell or memory B-cell immunity studies to examine the underlying mechanism. There are a variety of other immunosuppressant medications used. Similar concerns exist as to their effect on vaccine immunogenicity, but there are currently no strong data and it is difficult to extrapolate from methotrexate to other drugs. Nevertheless, American College of Rheumatology have long recommended a break from immune-suppressive DMARDs for one to two weeks after COVID-19 vaccination based on expert opinion [8].

This study adds to the literature showing that a temporary hold of methotrexate improves response to primary and booster vaccinations against COVID-19 [3-5]. This is an important issue as the COVID-19 pandemic is ongoing globally. As a result of emerging evidence [4], the British Society of Rheumatology have changed their guidance to support a temporary hold of methotrexate post-vaccine [9].

Further COVID-19 vaccine boosters are planned for high-risk individuals in many countries. As our patients are recommended to get both influenza and COVID-19 vaccinations regularly, it is reasonable to organise these vaccines to be administered together allowing patients to take a single two-week break from their methotrexate (in consultation with their specialist) after vaccination rather than the risk of multiple periods off treatment [10]. Future research is needed to provide additional evidence on the benefits and risks from holding other immunosuppressant drugs in the context of vaccination to best protect our rheumatology patients.

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