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.

Influenza vaccination and interruption of methotrexate in adult patients in the COVID-19 era: an ongoing dilemma

With the COVID-19 pandemic continuing unabated and the advent of the influenza season, public health authorities have emphasised that influenza vaccination is of paramount importance.[1] Vaccination can reduce the severity of influenza infection and prevent hospitalisations,[1] which might help to conserve already strained health-care resources. The European League Against Rheumatism recommends that annual influenza vaccination should be strongly considered for most patients with chronic autoimmune inflammatory rheumatic diseases, as these patients are at increased risk of infection due to inherent or iatrogenic immunocompromise.[2] There is no optimal formulation (valency or dose) of inactivated influenza vaccine for patients with autoimmune inflammatory rheumatic diseases. These patients require potentially lifelong immunosuppression, and short-term interruption of immunomodulation might sometimes be necessary to restore immune responses (eg, with severe infection or major surgery). Anecdotally, some clinicians temporarily discontinue methotrexate (eg, one week before or after immunisation) in patients with rheumatoid arthritis to optimise the efficacy of influenza vaccination, although this approach is not supported by guidelines. In this Comment, we consider the evidence base for and implications of this strategy during the COVID-19 pandemic.

Seasonal influenza is a major global cause of morbidity, mortality, and burden on health-care services. Influenza might be clinically confused with COVID-19, and co-infection carries a poor prognosis.[3] Influenza vaccination reduces the incidence of and complications, hospital admissions, and mortality from influenza and pneumonia in patients with autoimmune inflammatory rheumatic diseases.[2] The host immune system (including immunosenescence with ageing) might influence vaccine efficacy. Methotrexate is the most commonly prescribed first-line disease modifying anti-rheumatic drug (DMARD) for patients with rheumatoid arthritis, either alone or in combination with biological therapy. The immunosuppressive effect of methotrexate is beneficial in patients with rheumatoid arthritis to reduce biologic-associated immunogenicity (anti-drug antibodies),[4] but might compromise vaccine responses.[5]

The effects of temporary discontinuation of methotrexate on antibody titres to the trivalent influenza vaccine were investigated in a prospective, randomised, parallel-group, single-blind, single-centre pilot study of 199 patients with rheumatoid arthritis who were taking stable methotrexate doses (appendix).[6] Patients were randomly assigned to continue methotrexate (group 1; 54 patients), suspend methotrexate 4 weeks before vaccination (group 2; 44 patients), suspend methotrexate 2 weeks before and 2 weeks after vaccination (group 3; 49 patients); or suspend methotrexate 4 weeks after vaccination (group 4; 52 patients).[6] All groups showed a similar frequency of satisfactory vaccine responses (≥4-times increase in antibody titre); however, group 3 achieved significantly higher vaccine responses compared with group 1. Withholding methotrexate 4 weeks before influenza vaccination (group 2) was not associated with significantly different antibody titres, whereas discontinuing methotrexate for 4 weeks after vaccination (group 4) resulted in improvement compared with group 1. To reduce the risk of rheumatoid arthritis flares while achieving an adequate vaccine response, a shorter methotrexate discontinuation period was investigated in a prospective, multicentre study, in which patients with rheumatoid arthritis on stable methotrexate doses were randomly assigned to continue methotrexate (156 patients) or withhold methotrexate for 2 weeks (160 patients) after the quadrivalent influenza vaccine.[7] Significantly more patients in the methotrexate-hold group achieved satisfactory vaccine responses (≥4-times increase in antibody titre to at least two of four influenza antigens) compared with the methotrexate-continue group (75·5% *vs* 54·5%; p<0.001; difference 21·0%, 95% CI 10·6–31·7%). Neither of these studies showed a significant increase in rheumatoid arthritis flares after discontinuation of methotrexate.[6,7] A post-hoc analysis of these studies compared disease activity between the methotrexate-hold groups (for 4 weeks before[6] [44 patients] or two weeks after[7] [160 patients] vaccination) with a pooled methotrexate-continue group (210 patients).[8] The analysis concluded that short-term discontinuation of methotrexate for 2 weeks was safe, whereas discontinuation for 4 weeks was associated

Shutterstock

Published **Online**
November 10, 2020
https://doi.org/10.1016/S2665-9913(20)30392-1

See **Online** for appendix

with a transient increase in disease flares, although adjusted flare rates were 2·90 (2-week hold) and 3·94 (4-week hold).[8] However, only one group (group 2) from the first study was included and flare rate was based on disease activity measured at a single fixed timepoint, 4 weeks after methotrexate interruption. This timepoint corresponded to the end of the 4 week interruption period in the first study and 2 weeks after methotrexate resumption in the second study. The original studies did not show significantly increased rheumatoid arthritis flare rates with methotrexate interruption, and transient disease activity increases were readily controlled. Vaccine responses were more than 70% higher in the second study, even with methotrexate continuation (appendix).

It is unclear whether antibody titres to influenza vaccines (often used as the sole surrogate outcomes for efficacy) translate into protection from infection, or if there are better correlates in immunocompromised patients (eg, T-cell responses).[9] Although the risks of rheumatoid arthritis flare and need for glucocorticoids appear small, both can increase infection risk. Patients with autoimmune inflammatory rheumatic diseases receiving prednisolone at 10 mg or more had significantly poorer COVID-19 outcomes.[10] Furthermore, the generalisability of these studies (both from Korea) with low baseline methotrexate doses (10–15 mg weekly) is unclear.[6,7] The influence of patient age, methotrexate dose and administration route, duration and degree of rheumatoid disease activity, and other confounders (including smoking, alcohol consumption, and obesity) is also unclear. A large multicentre, international study would be required to confirm whether transient methotrexate interruption around the time of vaccination reduces incidence or severity of influenza, as well as the optimal strategy to achieve this.

Although a 2-week discontinuation of methotrexate after vaccination in patients with quiescent disease might improve influenza vaccine responses without a substantial impact on rheumatoid arthritis disease activity,[6–8] there is insufficient evidence to alter clinical practice or guidelines. Some patients had rheumatoid arthritis flares due to restricted access to health care during the initial COVID-19 pandemic, and interrupting methotrexate treatment might risk destabilising disease control. Nonetheless, we feel that the available evidence merits individualised discussions with patients with well-controlled disease regarding the potential benefits and risks of omission of 1–2 doses of methotrexate, influenza vaccine efficacy, and perhaps COVID-19 vaccination when available.

PM is a Medical Research Council (MRC)-GSK EMINENT clinical training fellow with project funding outside the submitted work. PM receives co-funding from the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre (UCLH BRC). PM has served on an advisory board for SOBI, outside the submitted work. RCC reports grants from UK Research and Innovation MRC, grants from GSK, and grants from NIHR ULCH BRC. CC receives co-funding from the UCLH BRC (525, 773) and Versus Arthritis (21593). JDI is a NIHR Senior Investigator and is supported by the Newcastle NIHR Biomedical Research Centre in Ageing and Long-Term Conditions. All other authors declare no competing interests. CC and JDI contributed equally to this Comment.

Puja Mehta, Emilie Sanchez, Elena Moraitis, Nicky Longley, Dennis W Lendrem, Ian P Giles, Rachel C Chambers, Coziana Ciurtin, John D Isaacs
puja.mehta@ucl.ac.uk

Centre for Inflammation and Tissue Repair, UCL Respiratory (PM, RCC), Centre for Rheumatology Research (IPG), and Centre for Adolescent Rheumatology (CC), Division of Medicine, University College London, WC1E 6JF London, UK; Department of Clinical Virology (ES) and Department of Rheumatology (PM, IPG), University College London Hospital (UCLH), London, UK; Hospital for Tropical Diseases, UCLH and London School of Hygiene & Tropical Medicine, London, UK (NL); Rheumatology Department, Great Ormond Street Hospital for Children, London, UK (EM); Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK (DWL, JDI); and Musculoskeletal Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK (DWL, JDI)

1 Jaklevic MC. Flu vaccination urged during COVID-19 pandemic. *JAMA* 2020; **324:** 926–27.
2 Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; **79:** 39–52.
3 Iacobucci G. Covid-19: Risk of death more than doubled in people who also had flu, English data show. *BMJ* 2020; **370:** m3720.
4 Mehta P, Manson JJ. What is the clinical relevance of TNF inhibitor immunogenicity in the management of patients with rheumatoid arthritis? *Front Immunol* 2020; **11:** 589.
5 Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2014; **66:** 1016–26.
6 Park JK, Lee MA, Lee EY, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2017; **76:** 1559–65.
7 Park JK, Lee YJ, Shin K, et al. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2018; **77:** 898–904.
8 Park JK, Kim MJ, Choi Y, Winthrop K, Song YW, Lee EB. Effect of short-term methotrexate discontinuation on rheumatoid arthritis disease activity: post-hoc analysis of two randomized trials. *Clin Rheumatol* 2020; **39:** 375–79.
9 McElhaney JE, Xie D, Hager WD, et al. T cell responses are better correlates of vaccine protection in the elderly. *J Immunol* 2006; **176:** 6333–39.
10 Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; **79:** 859–66.