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Flare of rheumatoid arthritis after COVID-19 vaccination



With the COVID-19 pandemic, there has been great uncertainty about whether the virus could exacerbate autoimmune diseases such as rheumatoid arthritis given that infection can lead to an overactivation of the immune system, which is thought to play a part in severe cases in the general population.^{1,2} A review of the literature shows there has been one case report so far of a flare of rheumatoid arthritis after infection with SARS-CoV-2.³

Three COVID-19 vaccines have been approved for emergency use in the USA so far.⁴ Two of the vaccines, BNT162b2 (BioNTech-Pfizer) and mRNA-1273 (Moderna), are novel mRNA-based vaccines delivered via lipid nanoparticles. The clinical trials of these vaccines allowed for patients with rheumatic disease to participate in the later stages of the trials, but excluded patients on immunosuppressive agents.^{5,6} Therefore, it is not fully known whether these vaccines might provoke flares of underlying rheumatic conditions as a result of immune activation or non-specific adjuvant effects. There are reports of other vaccines, such as those against tetanus, rubella, hepatitis B, and influenza, triggering rheumatoid arthritis, but causality has never been proven and an association has never been reproduced in large, controlled studies.⁷ Molecular mimicry is thought to be one mechanism by which autoimmunity can occur, in which similarities between viral peptides and self-peptides can stimulate immune activation, but this has not been proven in rheumatoid arthritis.⁸ The American College of Rheumatology issued guidance regarding COVID-19 vaccination on Feb 8, 2021, and acknowledged a theoretical risk of flare of autoimmune disease after vaccination with moderate consensus.⁹

Here, we present a case of a White male, aged 55 years, with non-erosive, seropositive rheumatoid arthritis (positive for rheumatoid factor, anticyclic citrullinated peptide antibodies, antinuclear antibodies, and anti-Ro antibodies) who had been in sustained clinical remission for more than 2 years and developed an acute flare of his rheumatoid arthritis 12 h after the second BNT162b2 vaccination.

The patient had been in clinical remission on upadacitinib monotherapy since July, 2018. At his last clinic visit in September, 2020, his physical exam showed no active synovitis or joint effusions, and his disease activity scores were consistent with remission

(clinical disease activity index=0; disease activity score of 28 joints with C-reactive protein=1.21). The patient had no known exposures to SARS-CoV-2 and had tested negative for SARS-CoV-2 by PCR in April, 2020, when screened for work. He received the first BNT162b2 vaccine on Dec 23, 2020, after which he developed minor arthralgias that resolved within 1 day. He received the second vaccine dose on Jan 13, 2021, and within 12 h developed clinically significant pain and swelling in the right knee. He had no other joint pain, swelling, or stiffness. He took ibuprofen and prednisone 5 mg soon after the pain and swelling began, but his symptoms persisted, so he contacted our office the next day and we advised him to increase his prednisone to 10 mg daily. Despite the increased medication, he continued to have clinically significant symptoms, so we asked him to come to our clinic for an ultrasound evaluation. He had continued on his usual rheumatoid arthritis treatment between the two vaccinations.

The patient came to our clinic on Jan 22, 2021—30 days after receiving the first BNT162b2 vaccination, and 9 days after the second vaccination—he had clinically significant swelling and warmth over the right knee with pain on flexion and extension of the knee. There was no tenderness, swelling, or erythema of any other joints. Ultrasound evaluation of the right knee showed a moderate to large compressible hypoechoic effusion in the suprapatellar recess that extended from the suprapatellar bursa proximally 5.2 cm deep to the quadriceps tendon and involved the medial and lateral gutter (appendix). There was increased power Doppler signal in the effusion in the lateral gutter. Additionally, there was a large effusion in the posterior knee deep to the semimembranosus tendon, consistent with a popliteal cyst.

Arthrocentesis of the right knee showed 24 mL of inflammatory-appearing effusion (appendix). Synovial fluid studies showed a cell count of 24,385 cells per μL , of which 62% were neutrophils, 30% were monocytes, 8% were lymphocyte, and none were eosinophils. Crystal exam was negative, and no organisms were identified on bacterial or fungal cultures. He had a normal complete metabolic panel and complete blood count, elevated C-reactive protein (8.0 mg/L; increased from 0.3 mg/L on Sept 9, 2020), and erythrocyte sedimentation rate

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39 mm/h (28 mm/h on June 10, 2020). The patient tested negative for SARS-CoV-2 IgG antibody on day 30, but subsequently tested positive on Feb 3, 2021 (42 days after his first vaccination).

His rheumatoid arthritis was well controlled before the vaccination, and there were no other inciting events, so we believe that this flare might have been triggered by his immune response to a component of the BNT162b2 vaccine. BNT162b2 contains mRNA encoding for the SARS-CoV-2 spike protein encapsulated in lipid nanoparticles, in addition to other components that stabilise the vaccine in the circulation and promote its uptake into cells by endocytosis. Although the mechanism of flare is not known, one could speculate that one of these components might have had non-specific adjuvant effect, or there could have been molecular mimicry between the viral spike peptides and the patient's self-peptides, activating a flare. However, we cannot exclude the possibility that the timing of the flare with regard to vaccination was coincidental. The patient was treated with intra-articular steroids with rapid improvement, and he is once again in clinical remission.

SARS-CoV-2 infection has resulted in more than 500 000 deaths in the USA and 2 500 000 worldwide (see the Coronavirus Resource Center). Given the high efficacy of the COVID-19 vaccines, the benefits of

vaccinating vulnerable populations outweigh the risk of rheumatic disease flare, and expert panels including the American College of Rheumatology continue to recommend the vaccine in all eligible patients.^{5,9}

The patient provided informed consent to publish this case. KAT and FKT both contributed to direct care of the patient. KAT authored the paper with edits made by FKT. We declare no competing interests.

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- 1 Kalfaoglu B, Almeida-Santos J, Tye CA, Satou Y, Ono M. T-cell hyperactivation and paralysis in severe COVID-19 infection revealed by single-cell analysis. *Front Immunol* 2020; **11**: 589380.
- 2 Silva TF, Tomiotto-Pellissier F, Sanfelice RA, et al. A 21st century evil: immunopathology and new therapies of COVID-19. *Front Immunol* 2020; **11**: 562264.
- 3 Perrot L, Hemon M, Busnel JM, et al. First flare of ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection. *Lancet Rheumatol* 2021 **3**: e6-8.
- 4 US Centers for Disease Control and Prevention. Understanding m-RNA COVID-19 vaccines. Dec 18, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html> (accessed Jan 28, 2021).
- 5 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020 **383**: 2603-15.
- 6 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384**: 403-16.
- 7 Ray P, Black S, Shinefield H, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15-59 years of age. *Vaccine* 2011; **29**: 6592-97.
- 8 Rojas M, Restrepo-Jiménez P, Monsalve DM, et al. Molecular mimicry and autoimmunity. *J Autoimmun* 2018; **95**: 100-23.
- 9 American College of Rheumatology. COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases. March 4, 2021. <https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf> (accessed Feb 20, 2021).



Anti-SARS-CoV-2 mRNA vaccine in patients with rheumatoid arthritis

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Long-term vaccine-induced immunity is crucial for controlling the COVID-19 pandemic. Vaccination against COVID-19 is recommended for patients with rheumatic diseases, but a paucity of data are available regarding COVID-19 vaccines in patients with rheumatoid arthritis. Because patients receiving immunosuppressive treatment were excluded from the phase 3 clinical trials,^{1,2} it is not clear whether disease-modifying anti-rheumatic drug (DMARD) treatment should be continued before and after vaccination. In addition, some published reports are limited to follow-up after a single vaccine dose.³⁻⁵

Here we report 53 consecutive patients with rheumatoid arthritis on DMARDs and 20 healthy

controls (appendix p 1) who were eligible for vaccination according to the Swiss federal regulations and were enrolled in the RECOVER study, a non-randomised, prospective, observational trial. The RECOVER study was approved by the Ethical Committee of St Gallen, Switzerland, and written consent was obtained from all patients before inclusion. The vaccination itself was not part of the study. Nine patients received two doses of the mRNA-1273 vaccine (Moderna), all others received two doses of the BNT162b2 vaccine (Pfizer-BioNTech). Serum samples were collected at baseline, 3 weeks after the first vaccination, and 2 weeks after the second vaccination. Quantitative antibody testing was done using the Roche Elecsys Anti-SARS-CoV-2 spike