Breakthrough infection after three doses of COVID-19 mRNA vaccine in systemic autoimmune rheumatic diseases: two cases in patients on TNF inhibitor monotherapy

Kathleen MM Vanni,¹ Naomi J Patel,² Michael Dilorio,³ Emily Kowalski,¹ Grace Qian,¹ Claire E Cook,² Susan Y Ritter,^{1,4} Zachary S Wallace,^{2,4} Jeffrey A Sparks ^{1,4}

To cite: Vanni KMM, Patel NJ, Dilorio M, *et al.* Breakthrough infection after three doses of COVID-19 mRNA vaccine in systemic autoimmune rheumatic diseases: two cases in patients on TNF inhibitor monotherapy. *RMD Open* Published Online First: [please include Day Month Year]. doi:10.1136/rmdopen-2021-002082

ZSW and JAS are joint senior authors.

Accepted 12 November 2021

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¹Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Boston, Massachusetts, USA

²Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Boston, Massachusetts, USA

³Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁴Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to

Dr Jeffrey A Sparks;
jsparks@bwh.harvard.edu

Despite COVID-19 vaccination, immunocompromised patients may be particularly susceptible to SARS-CoV-2 breakthrough infections,¹ defined by the US Centers for Disease Control and Prevention (CDC) as positive test results 14 or more days after initial vaccine series completion (<https://www.cdc.gov/vaccines/COVID-19/health-departments/breakthrough-cases.html>). On 13 August 2021, the US Food and Drug Administration and CDC authorised immunocompromised patients to receive a third dose of SARS-CoV-2 mRNA vaccine, defining this as the completion of their initial series (rather than a 'booster'). Studies have evaluated breakthrough infections in patients with systemic autoimmune rheumatic diseases (SARDs) after the second but not third dose of mRNA (messenger ribonucleic acid) vaccine.^{2,3} Therefore, we aimed to provide an early description of two cases of breakthrough infections occurring after three mRNA vaccine doses.

Mass General Brigham (MGB) is a large, multicentre healthcare system in the greater Boston, Massachusetts area. As previously described,⁴ we systematically identify all patients with SARDs at MGB with confirmed COVID-19 (by PCR or antigen testing). As of 25 October 2021, we identified two cases of breakthrough infections at least 14 days after receipt of three mRNA vaccine doses (table 1).

The first case is a 31-year-old woman with a history of juvenile idiopathic arthritis diagnosed at age 8 that evolved into seronegative inflammatory arthritis in adulthood. Her inflammatory arthritis was in remission on adalimumab. She had no other comorbidities, never smoked and was on no other

medications. She received mRNA-1273 (Moderna) vaccine doses on 29 January 2021, 26 February 2021 and 22 August 21. Thirty days later, she developed cough, headache, malaise, fever, diarrhoea, anosmia and dysgeusia. She presented and tested positive for SARS-CoV-2 by antigen test. Given her immunocompromised state, she received monoclonal antibody treatment (casirivimab/imdevimab) 2 days after the positive test. Symptoms resolved without need for hospitalisation.

The second case is a 51-year-old man with seropositive rheumatoid arthritis of 14 years duration. He was in remission on certolizumab pegol. He also had hypertension, hyperlipidaemia, obesity and obstructive sleep apnoea. Other medications were gabapentin, olmesartan/hydrochlorothiazide, rosuvastatin and finasteride. He received Pfizer-BioNTech (BNT162b2) doses on 21 January 2021, 11 February 2021 and 25 August 2021. Fourteen days later, he developed chest pain and then fever, sore throat and dry cough that prompted PCR testing for SARS-CoV-2 that was positive 16 days after the third vaccine dose. His spouse also had COVID-19 that was diagnosed the day before his test. He received supportive care and never required hospitalisation.

To our knowledge, these are the first reports of SARS-CoV-2 infection after three doses of mRNA, the current standard initial vaccine series for immunocompromised individuals. Our findings may be reassuring since both patients had a mild COVID-19 course. Some breakthrough infections are expected for any vaccine. The number of patients with SARD within MGB who had received three mRNA

Table 1 Characteristics of two cases of breakthrough SARS-CoV-2 infections 14+days after the third dose of mRNA vaccine

	Case 1	Case 2
Type of SARS-CoV-2 vaccine	mRNA-1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)
Date of mRNA vaccine #1	29 January 2021	21 January 2021
Date of mRNA vaccine #2	26 February 2021	11 February 2021
Date of mRNA vaccine #3	22 August 2021 (T)	25 August 2021 (T)
Date of breakthrough testing and type	23 September 2021 Antigen test (Lumiradx)	10 September 2021 qRT-PCR
Time from third mRNA dose to SARS-CoV-2 positive test	T+32 days	T+16 days
Days from symptom onset to SARS-CoV-2 positive test	1 day	2 days
Age at breakthrough infection	31 years	51 years
Sex	Female	Male
Race/ethnicity	White	White
Type of SARD	Juvenile idiopathic arthritis/seronegative inflammatory arthritis	Seropositive rheumatoid arthritis
SARD duration	23 years	14 years
Immunosuppressive medications	Adalimumab 40 mg SC every other week	Certolizumab pegol 200 mg SC every other week
Smoking status	Never smoker	Never smoker
Comorbidities	None	Hypertension, hyperlipidaemia, obesity, obstructive sleep apnoea
Body mass index (kg/m ²)	24.1	35.6
Symptoms of COVID-19	Rhinorrhoea, sore throat, dry cough, fever, fatigue, headache, diarrhoea, dysgeusia, anosmia	Fever, sore throat, dry cough, chest pain
Treatment of COVID-19	Monoclonal antibody (casirivimab/imdevimab) on T+34 days	Supportive care
COVID-19 severity and course	Not hospitalised/fully recovered	Not hospitalised/fully recovered

mRNA, messenger ribonucleic acid; SARD, systemic autoimmune rheumatic disease; SC, subcutaneous.

doses is unavailable, so we cannot determine rates of breakthrough infection after three mRNA vaccine doses in this population. Additionally, spike antibody titres and whether tumour necrosis factor inhibitors (TNFi) were temporarily discontinued around vaccination are unknown. Both patients were being treated with TNFi as monotherapy at the time of COVID-19 onset, without other immunosuppressive medications or serious underlying comorbidities. A recent report suggested that

TNFi users at time of COVID-19 vaccination may mount insufficient immune responses to the SARS-CoV-2 delta variant,⁵ the predominant circulating strain in Massachusetts (and worldwide) at the time of both patients' infections. The American College of Rheumatology COVID-19 Vaccine Clinical Guidance Task Force recently 'could not achieve consensus' on whether to hold cytokine inhibitors such as TNFi at the time of third mRNA vaccine dose.⁶ These findings support further research into determining whether biological disease-modifying antirheumatic drugs such as TNFi should be temporarily discontinued around COVID-19 vaccination to optimise immune response to the delta as well as future variants.

Acknowledgements We thank each patient and their providers.

Contributors All authors made substantial contributions to the conception or design of the work and in the acquisition, analysis and interpretation of the data. All authors drafted or revised the work for critically important intellectual consent. All authors provided final approval of the version to be published.

Funding NJP is supported by the National Institutes of Health Ruth L. Kirschstein Institutional National Research Service Award (T32 AR007258). ZSW is funded by NIH/NIAMS (K23AR073334 and R03AR078938). JAS is funded by NIH/NIAMS (grant numbers R01 AR077607, P30 AR070253, and P30 AR072577) and the R. Bruce and Joan M. Mickey Research Scholar Fund.

Competing interests ZSW reports research support from Bristol Myers Squibb and Principia/Sanofi and consulting fees from Viela Bio and MedPace. All other authors report no competing interests. JAS has received research support from Bristol Myers Squibb and performed consultancy for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Inova Diagnostics, Janssen, Optum and Pfizer unrelated to this work.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study was approved by Mass General Brigham IRB (Protocol #: 2020P000840).

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD

Jeffrey A Sparks <http://orcid.org/0000-0002-5556-4618>

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