


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

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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.

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