Clinical characteristics and outcomes of COVID-19 breakthrough infections among vaccinated patients with systemic autoimmune rheumatic diseases

SARS-CoV-2 vaccines reduce the risk of COVID-19.[1–3] However, some disease-modifying anti-rheumatic drugs (DMARDs), particularly glucocorticoids, methotrexate, mycophenolate mofetil and rituximab, may blunt the immunological response to COVID-19 vaccination.[4] Little is known about the clinical efficacy of these vaccines at preventing COVID-19 infection in patients with systemic autoimmune rheumatic diseases (SARDs).

Mass General Brigham (MGB) is a large multicentre healthcare system in the Boston, Massachusetts, USA area. Patients with SARDs with a positive SARS-CoV-2 PCR or antigen test between 30 January 2020 and 30 July 2021 at MGB were identified using diagnostic billing codes or were referred by physicians, as previously described.[5] From this cohort, we identified breakthrough infections in fully vaccinated patients, defined as a positive test ≥14 days after the final vaccine dose.[6]

Of 786 SARD patients with COVID-19, 340 occurred after the initial emergency use authorisation for COVID-19 vaccination in the USA. Of these, 16 (4.7%) were breakthrough infections (online supplemental figure 1). Among the breakthrough infections, 12 (75%) were female, 11 (69%) were white, the median age was 50 years and 12 (75%) had ≥1 comorbidity (table 1). The most common SARDs included rheumatoid arthritis (6, 38%), inflammatory myositis (3, 19%) and systemic lupus erythematosus (3, 19%). Rituximab (5, 31%), glucocorticoids (5, 31%), mycophenolate mofetil or mycophenolic acid (4, 25%) and methotrexate (3, 19%) were the most frequent immunosuppressives recorded prior to first vaccine dose. One (6%) patient was on no DMARD or glucocorticoid at the time of his/her vaccine.

Seven (44%) patients received the BNT162b2 (Pfizer-BioNtech) vaccine, five (31%) received the mRNA-1273 (Moderna) vaccine and four (25%) received the AD26.COV2.S (Janssen/Johnson & Johnson) vaccine. The median time from final vaccine dose to infection was 54 days (table 1). Among the 16 breakthrough infections, 15 (93%) were symptomatic and 6 (38%) patients were hospitalised, during which 4 (25%) required supplemental oxygen and 1 (6%) required mechanical ventilation (online supplemental table 1). DMARDs used prior to infection among hospitalised patients included rituximab (4, 25%) and mycophenolate mofetil or mycophenolic acid (2, 13%). Two (13%) patients died; both deceased patients had received rituximab and had interstitial lung disease.

In conclusion, a small portion of COVID-19 cases among patients with SARDs in a large US healthcare system occurred among fully vaccinated patients. However, some patients required hospitalisation that ultimately culminated in death. The most common SARD treatments at the time of vaccination included those associated with blunted antibody responses to SARS-CoV-2 vaccination.[4] These findings suggest that the blunted SARS-CoV-2 antibody response following COVID-19 vaccination in certain DMARD users may be associated with an increased risk of breakthrough infections that may be severe and even fatal. Of note, the blunted response observed among glucocorticoid users is dose dependent, especially above 10 mg/day of prednisone. Some DMARD users may require

Table 1 Patient characteristics, vaccination details, medication use and infection details of COVID-19 breakthrough infections in fully vaccinated patients with SARDs (nN=16)

Patient characteristics	n, %
Female	12, 75
Age (median, IQR)	49.5 (38.0–64.5)
Race	
White	11, 68
Black	3, 20
Hispanic	2, 13
Rheumatic disease*	
Rheumatoid arthritis	6, 38
Rheumatoid arthritis-associated interstitial lung disease	1, 6
Dermatomyositis	3, 19
Myositis-associated interstitial lung disease	1, 6
Systemic lupus erythematosus	3, 19
Ankylosing spondylitis	2, 13
IgG4-related disease	1, 6
Mixed connective tissue disease	1, 6
Hypocomplementemic urticarial vasculitis	1, 6
Psoriatic arthritis	1, 6
Comorbidities*	
Hypertension	6, 38
Morbid obesity (BMI ≥40.0 kg/m^2)	3, 19
Interstitial lung disease	2, 13
End-stage renal disease	2, 13
Chronic obstructive pulmonary disease	1, 6
Asthma	1, 6
Diabetes	1, 6
Obesity (BMI ≥30.0 kg/m^2)	1, 6
Coronary artery disease	1, 6
Cancer	1, 6
Organ transplant	1, 6
Immunodeficiency	1, 6
Chronic neurological or neuromuscular disease	1, 6
Inflammatory bowel disease	1, 6
None	4, 25
Smoking status	
Current	1, 6
Former	7, 44
Never	6, 38
Unknown	2, 13
Vaccination details	**n, %**
Vaccine type	
Pfizer-BioNtech	7, 44
Moderna	5, 31
Janssen/Johnson & Johnson	4, 25
Disease activity at vaccination	
First vaccination	
Active	5, 31
Inactive	11, 69
Second vaccination	
Active	6, 38
Inactive	6, 38
Not applicable	4, 25
Rheumatic disease treatment use prior to first vaccine dose†	**n, %**
Rituximab	5, 31
Glucocorticoids	5, 31
Mycophenolate mofetil or mycophenolic acid	4, 25
Methotrexate	3, 19
Tacrolimus	2, 13
Adalimumab	1, 6

Continued

Table 1 Continued

Patient characteristics	n, %
Azathioprine	1, 6
Belimumab	1, 6
Hydroxychloroquine	1, 6
Intravenous immunoglobulin	1, 6
Sulfasalazine	1, 6
Tocilizumab	1, 6
Ustekinumab	1, 6
None	1, 6
COVID-19 infection details	**n, %**
Time (days) from second/final vaccine dose to infection (median, IQR)	54.0 (29.8–79.0)
Infection acquisition	
Close contact with confirmed or probable case of COVID-19	4, 25
Presence in a healthcare facility with COVID-19 cases	3, 19
Community acquired	3, 19
Unknown	8, 50
Treatment	
No treatment/supportive care only	7, 44
Remdesivir	6, 38
Glucocorticoids	3, 19
Neutralising monoclonal antibody	4, 25
Azithromycin	2, 13
Convalescent plasma	1, 6
Enrolled in clinical trial‡	1, 6
Any symptoms	
Yes	15, 93
No§	1, 6
Symptoms	
Fever	9, 56
Cough	7, 44
Malaise	6, 38
Myalgia	5, 31
Rhinorrhea	5, 31
Headache	4, 25
Shortness of breath	4, 25
Sore throat	4, 25
Diarrhoea/vomiting/nausea	3, 19
Anosmia	3, 19
Dysgeusia	3, 19
Chest pain	2, 13
Arthralgia	1, 6
Other	1, 6
Outcomes¶	**n, %**
Outpatient management alone	10, 63
Hospitalisation	6, 38
Ventilation	1, 6
Death	2, 13
Unresolved symptoms	2, 13

*Patients may have >1 SARD or comorbidity.
†One patient initiated methotrexate in between the first and second dose and one patient initiated rituximab between the second dose and infection.
‡NCT04501978; phase 3 randomised, blinded, trial assessing treatments for hospitalised patients with COVID-19. Intervention arms: investigational drug +standard of care (remdesivir) or placebo +standard of care (remdesivir).
§Diagnosed via pre-procedure PCR test, no reported symptoms in electronic health record.
¶Symptoms were unresolved (one active infection recent diagnosed, one reporting ongoing symptoms: fatigue/malaise) in two (13%) cases.
BMI, body mass index; SARD, systemic autoimmune rheumatic disease.

alternative risk mitigation strategies, including passive immunity or booster vaccines and may need to continue shielding practices.

Our study has certain limitations. First, we did not study the risk of breakthrough infections among a cohort of vaccinated patients with a known denominator. Therefore, we cannot estimate the rate of breakthrough infections among patients with SARDs. It is possible that the observed number of cases might be expected since no vaccine will prevent every infection. Second, the proportion of asymptomatic breakthrough infections observed in our study may be an underestimate because we only included patients who presented for testing. Third, we did not have SARS-CoV-2 antibody testing available for all patients and cannot rule out the possibility that SARD manifestations (eg, interstitial lung disease) commonly treated with these medications contributed to the severity of the presentation.

In light of our findings, additional studies are urgently needed to estimate the risk of breakthrough infections among patients with SARDs and to evaluate the efficacy of booster vaccines and other strategies for DMARD users with poor immunological response to COVID-19 vaccination.

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REFERENCES

1 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.
2 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.
3 Sadoff J, Gray G, Vandebosch A, *et al*. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021;384:2187–201. doi:10.1056/NEJMoa2101544
4 Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. *Rheumatology* 2021;60:3496–502.
5 D'Silva KM, Serling-Boyd N, Hsu TY-T, *et al*. SARS-CoV-2 antibody response after COVID-19 in patients with rheumatic disease. *Ann Rheum Dis* 2021;80:817–9.
6 CDC COVID-19 Vaccine Breakthrough Case Investigations Team. COVID-19 Vaccine Breakthrough Infections Reported to CDC - United States, January 1-April 30, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:792–3.