

## 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.<sup>1-3</sup> However, some disease-modifying anti-rheumatic drugs (DMARDs), particularly glucocorticoids, methotrexate, mycophenolate mofetil and rituximab, may blunt the immunological response to COVID-19 vaccination.<sup>4</sup> 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.<sup>5</sup> From this cohort, we identified breakthrough infections in fully vaccinated patients, defined as a positive test  $\geq 14$  days after the final vaccine dose.<sup>6</sup>

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  $\geq 1$  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/Johanson & 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.<sup>4</sup> 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 $\geq 40.0$ kg/m <sup>2</sup> )	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 $\geq 30.0$ kg/m <sup>2</sup> )	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/Johanson & 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
Rhinorrhoea	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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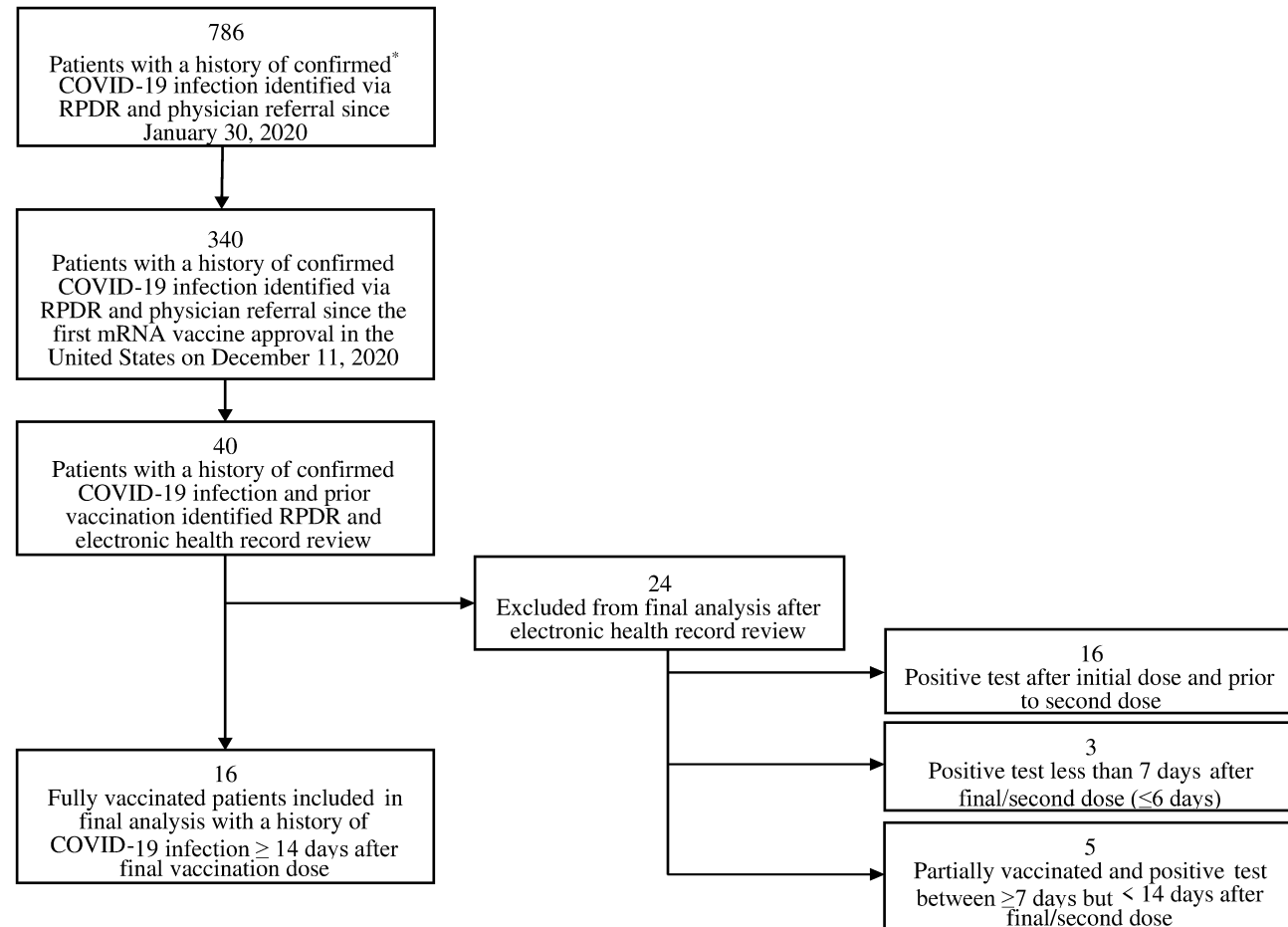
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**Supplemental Figure 1.** Identification of COVID-19 breakthrough infections among vaccinated patients with systemic autoimmune rheumatic diseases



RPDR, Research Patient Data Registry

\*Confirmed with positive SARS-CoV-2 polymerase chain reaction or antigen test

**Supplementary Table 1.** Descriptions of COVID-19 breakthrough infections  $\geq 14$  days after second/final vaccine dose among patients with systemic rheumatic diseases (n=16)

Case	Age range	Rheumatic Disease	Vaccine Type	Time from final vaccine to diagnosis (days)	Rheumatic disease treatment at the time of first vaccine dose	Rheumatic disease treatment at the time of second vaccine dose (if different/new from first)	Time from last B cell depletion before vaccination to first vaccine dose (days)	Asymptomatic infection	COVID-19 treatment	Hospitalization	Supplemental oxygen/mechanical ventilation	Deceased
1	45-64	Dermatomyositis	Moderna	16	Azathioprine, Rituximab		99	No	Remdesivir, azithromycin, glucocorticoids	Yes	Supplemental oxygen	No
2	45-64	Systemic lupus erythematosus	Pfizer-BioNTech	24	Mycophenolate Moferil, Tacrolimus, Prednisone (5mg/d)			No	Remdesivir, Neutralizing monoclonal antibody	Yes	Supplemental oxygen	No
3	>85	Rheumatoid arthritis	Pfizer-BioNTech	26	Prednisone (10mg/d)	Methotrexate*		No	None	No	No	No
4	45-64	Hypocomplementemic urticarial vasculitis, Mixed connective tissue disease	Pfizer-BioNTech	29	Hydroxy-chloroquine, Methotrexate			No	None	No	No	No
5	25-44	Systemic lupus erythematosus	Moderna	30	Mycophenolic Acid, Belimumab			No	Remdesivir	Yes <sup>†</sup>	No	No
6	45-64	Rheumatoid arthritis	Janssen/Johnson & Johnson	33	None			Yes <sup>‡</sup>	None	No	No	No
7	65-84	Rheumatoid arthritis	Janssen/Johnson & Johnson	40	Rituximab		190	No	Remdesivir, glucocorticoids	Yes	Supplemental oxygen	No

8	45-64	Systemic lupus erythematosus	Pfizer-BioNTech	50	Mycophenolic acid, Tacrolimus			No	Neutralizing monoclonal antibody	No	No	No
9	65-84	Ankylosing spondylitis, Dermatomyositis with interstitial lung disease	Pfizer-BioNTech	57	Rituximab, prednisone (20mg/d)		25	No	Remdesivir, glucocorticoids, Convalescent plasma, Enrolled in clinical trial <sup>§</sup>	Yes	Supplemental oxygen and high-flow oxygen device	Yes
10	25-44	Dermatomyositis	Moderna	61	IVIg, Mycophenolate mofetil, Rituximab		111	No	None	No	No	No
11	25-44	Rheumatoid arthritis	Pfizer-BioNTech	70	Methotrexate			No	None	No	No	No
12	65-84	Rheumatoid arthritis-associated interstitial lung disease	Moderna	78	Rituximab		35	No	Remdesivir, azithromycin, glucocorticoids	Yes	Mechanical ventilation	Yes
13	25-44	IgG4-related disease	Moderna	82	Prednisone (10mg/d) <sup>¶</sup>			No	None	No	No	No
14	18-24	Rheumatoid arthritis	Pfizer-BioNTech	96	Methotrexate, Tocilizumab			No	Neutralizing monoclonal antibody	No	No	No
15	25-44	Ankylosing spondylitis	Janssen/Johnson & Johnson	111	Adalimumab, Sulfasalazine			No	None	No	No	No
16	25-44	Psoriatic arthritis	Janssen/Johnson & Johnson	132	Ustekinumab, prednisone (10mg/day)			No	Neutralizing monoclonal antibody	No	No	No

IVIg, Intravenous immunoglobulin

\* Initiated methotrexate between dose one and two

† Hospitalization unrelated to COVID-19 diagnosis

‡ Diagnosed via pre-procedure PCR test, no reported symptoms in electronic health record

§ NCT04501978; Phase 3 randomized, blinded, trial assessing treatments for hospitalized patients with COVID-19. Intervention arms: investigational drug + standard of care (Remdesivir) or placebo + standard of care (Remdesivir)

¶ Initiated rituximab between the second dose and infection

