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ORIGINAL RESEARCH

SARS-CoV-2 breakthrough infections among vaccinated individuals with rheumatic disease: results from the COVID-19 Global Rheumatology Alliance provider registry

Jean Liew ¹, Milena Gianfrancesco,² Carly Harrison,³ Zara Izadi ⁴, Stephanie Rush,⁵ Saskia Lawson-Tovey ^{6,7}, Lindsay Jacobsohn,² Clairissa Ja,⁸ Kimme L Hyrich,⁹ Laure Gossec ^{10,11}, Anja Strangfeld ¹², Loreto Carmona ¹³, Martin Schäfer ¹⁴, Elsa Frãzao-Mateus,¹⁵ Inita Bulina,¹⁶ Frances Stafford,¹⁷ Abdurrahman Tufan,¹⁸ Christine Graver,¹⁹ Gözde Kübra Yardımcı ^{20,21}, Julija Zepa,¹⁶ Samar Al Emadi,²² Claire Cook,²³ Fatemah Abutiban,²⁴ Dfiza Dey,^{25,26} Genevieve Katigbak,²⁷ Lauren Kaufman,²⁸ Emily Kowalski,²⁹ Marco Ulises Martínez-Martínez,^{30,31} Naomi J Patel,³² Greta Reyes-Cordero,³³ Evelyn Salido,³⁴ Ellison Smith,^{35,36} David Snow,³⁷ Jeffrey Sparks ³⁸, Leanna Wise,³⁹ Suleman Bhana,⁴⁰ Monique Gore-Massy,⁴¹ Rebecca Grainger,^{42,43} Jonathan Hausmann ^{44,45}, Emily Sirotich ⁴⁶, Paul Sufka,⁴⁷ Zachary Wallace,^{32,48} Pedro M Machado ^{49,50}, Philip C Robinson ^{51,52}, Jinoos Yazdany⁵³

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JL and MG contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Jean Liew;
liew.jw@gmail.com

ABSTRACT

Objective While COVID-19 vaccination prevents severe infections, poor immunogenicity in immunocompromised people threatens vaccine effectiveness. We analysed the clinical characteristics of patients with rheumatic disease who developed breakthrough COVID-19 after vaccination against SARS-CoV-2.

Methods We included people partially or fully vaccinated against SARS-CoV-2 who developed COVID-19 between 5 January and 30 September 2021 and were reported to the Global Rheumatology Alliance registry. Breakthrough infections were defined as occurring ≥ 14 days after completion of the vaccination series, specifically 14 days after the second dose in a two-dose series or 14 days after a single-dose vaccine. We analysed patients' demographic and clinical characteristics and COVID-19 symptoms and outcomes.

Results SARS-CoV-2 infection was reported in 197 partially or fully vaccinated people with rheumatic disease (mean age 54 years, 77% female, 56% white). The majority (n=140/197, 71%) received messenger RNA vaccines. Among the fully vaccinated (n=87), infection occurred a mean of 112 (± 60) days after the second vaccine dose. Among those fully vaccinated and hospitalised (n=22, age range 36–83 years), nine had used B cell-depleting therapy (BCDT), with six as monotherapy, at the time of vaccination. Three were on mycophenolate. The majority (n=14/22, 64%) were not taking systemic glucocorticoids. Eight patients had pre-existing lung disease and five patients died.

Conclusion More than half of fully vaccinated individuals with breakthrough infections requiring hospitalisation were on BCDT or mycophenolate. Further risk mitigation strategies are likely needed to protect this selected high-risk population.

INTRODUCTION

Despite the established efficacy of COVID-19 vaccines, breakthrough infections still occur in those who are vaccinated.^{1–3} There is particular concern for people on immunomodulatory and immunosuppressive medications, including those with rheumatic disease. Studies have shown that specific classes of medications (B cell-depleting therapy (BCDT), antimetabolites and glucocorticoids) can severely hamper the humoral response and have some impact on the T cell-mediated response.^{4–6} Due to accumulating data demonstrating reduced immune responses in some immunosuppressed individuals, several countries have amended vaccination programmes to offer an additional dose after completion of the primary vaccine series in this population.^{7–12}

Key messages

What is already known about this subject?

- ▶ COVID-19 vaccination is recommended and usually well tolerated and efficacious among people with rheumatic disease.
- ▶ However, laboratory-based studies using surrogate markers of protection against COVID-19 have demonstrated reduced vaccine immunogenicity, particularly humoral immunity, in people taking certain immunosuppressive medications.

What does this study add?

- ▶ Among fully vaccinated individuals with rheumatic disease who developed breakthrough SARS-CoV-2 infections, over half of patients requiring hospitalisation were treated with either B cell-depleting therapy or mycophenolate.
- ▶ Reassuringly, use of other immunomodulators including tumor necrosis factor (TNF) inhibitors was infrequent in this series.
- ▶ These data provide real-world evidence, corroborating results from laboratory-based studies of surrogate correlates of protection against COVID-19.

How might this impact on clinical practice or further developments?

- ▶ Breakthrough SARS-CoV-2 infection following vaccination is an ongoing concern for people with rheumatic diseases.
- ▶ These data add to the knowledge about which patients are at risk of vaccine failure and strengthen the rationale for additional vaccine doses and for secondary prevention of severe COVID-19 with monoclonal antibodies and other therapies.

Despite laboratory data regarding diminished antibody responses to vaccination, clinical data on breakthrough infections in people with rheumatic disease are sparse. Such data are important both to prioritise patient groups for additional vaccine doses and for guidance about use of other strategies, such as monoclonal antibodies or emerging antivirals against SARS-CoV-2, for postexposure prophylaxis or early treatment to prevent progression to severe COVID-19.

Given the need for data to inform public health measures and for counselling and care of immunocompromised patients in the clinical setting, we analysed the characteristics of people with rheumatic disease who developed COVID-19 following vaccination using the COVID-19 Global Rheumatology Alliance (C19-GRA) registry.

METHODS

The C19-GRA registry was launched on 24 March 2020 and allows healthcare providers globally to enter data on people with rheumatic disease diagnosed with COVID-19 via a REDCap survey.^{13 14} Registry data elements collected include provider name, city, country and clinic, and patient age, sex, race and ethnicity. Data include rheumatic disease medications, physician global assessment of disease activity (remission, low, moderate or high) and comorbidities at the time of COVID-19 diagnosis. We also included information on whether medications were held in online supplemental table 3. Data on COVID-19

include diagnosis date, symptoms, treatments and outcomes, with available laboratory results also collected.

On 5 January 2021, an initial set of vaccine-related questions were added to the registry, including whether patients had received a COVID-19 vaccine, which vaccine was received, how many doses and date of the most recent dose. Additional questions, related to timing of infection and specific rheumatic disease medications at the time of vaccination and whether they were held with each vaccine dose, were added on 8 July 2021. This study reports on people with breakthrough SARS-CoV-2 infection following vaccination who were entered into the registry between 5 January 2021 and 30 September 2021. The current analysis includes previously published cases from Lawson-Tovey *et al*¹⁵ (n=8) and Cook *et al*¹⁶ (n=16).

We analysed SARS-CoV-2 infection following vaccination reported to the registry, with a particular focus on individuals who were fully vaccinated, especially with regard to hospitalisation. We defined ‘partially vaccinated’ as being ≤ 14 days after the first dose in a two-dose series or within 13 days of a single-dose vaccine.¹⁷ Breakthrough infection among fully vaccinated individuals was defined according to the US Centers for Disease Control and Prevention (CDC) as infection occurring ≥ 14 days after the second dose in a two-dose series or ≥ 14 days after a single-dose vaccine.¹⁷ We excluded people with COVID-19 who were within 14 days of their first dose of a two-dose series (n=25) as the CDC definition considers these individuals to be unvaccinated. Continuous variables are reported as mean (SD). Categorical variables are reported as number and percentage. We used a histogram to visually assess time from vaccination to infection.

Patient and public involvement

As members of the C19-GRA, including its Steering Committee and Patient Board, patients were involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

We identified 110 partially and 87 fully vaccinated patients with rheumatic disease in the C19-GRA registry. Demographic and clinical characteristics of fully vaccinated individuals are shown in table 1; partially vaccinated individuals are described in online supplemental table 1. Fully vaccinated individuals (n=87) had a mean age of 54 years, and 77% were female and 56% were white. The majority (75%) were from North America. The most common rheumatic diseases were rheumatoid arthritis (39%), psoriatic arthritis (14%) and systemic lupus erythematosus (12%). At the time of infection, 34% were taking conventional synthetic disease-modifying antirheumatic drugs only, 28% biologic/targeted synthetic disease-modifying antirheumatic drugs only and 31% were on both; 7% of patients were not taking any disease-modifying antirheumatic drug. The majority (70%) were not on glucocorticoids; among those taking

Table 1 Demographic and disease characteristics of fully vaccinated* individuals with rheumatic disease diagnosed with SARS-CoV-2 infection after vaccination reported to the C19-GR registry (n=87)

	Frequency (%) or mean (SD)
Mean age (years), SD	53.8 (16.3)
Female	67 (77)
Race or ethnicity	
White	49 (56.3)
Black	6 (6.9)
Latin American	10 (11.5)
East or South Asian	7 (8.1)
Other	9 (10.3)
Unknown	6 (6.9)
WHO regions	
African region	2 (2.3)
Region of the Americas - North	65 (74.7)
Region of the Americas - South	1 (1.2)
South-East Asian region	0 (0)
European region	8 (9.2)
Eastern Mediterranean region	7 (8.1)
Western Pacific region	4 (4.6)
Rheumatic disease†	
Rheumatoid arthritis	34 (39.1)
Systemic lupus erythematosus	10 (11.5)
Psoriatic arthritis	12 (13.8)
Vasculitis	10 (11.5)
Inflammatory myopathy	8 (9.2)
Spondyloarthritis (axial and other)	3 (3.5)
Sjogren's syndrome	4 (4.6)
Systemic sclerosis	4 (4.6)
Other‡	8 (9.2)
Comorbidity count	
0	46 (52.9)
1	26 (29.9)
≥2	15 (17.2)
Most common comorbidities	
Hypertension	24 (27.6)
Obesity	18 (20.7)
Lung disease	16 (18.4)
Diabetes	9 (10.3)
Chronic kidney disease	8 (9.2)
Medication prior to COVID-19 diagnosis§	
No DMARD	6 (6.9)
csDMARDs	57 (65.5)
Methotrexate	21 (24.1)

Continued

Table 1 Continued

	Frequency (%) or mean (SD)
Hydroxychloroquine	25 (28.7)
Leflunomide	6 (6.9)
Azathioprine	6 (6.9)
Mycophenolate	10 (11.5)
Sulfasalazine	4 (4.6)
Colchicine	2 (2.3)
b/tsDMARDs	51 (58.6)
B cell-depleting therapy	16 (18.4)
TNF inhibitors	19 (21.8)
Other biologics¶	10 (11.5)
JAK inhibitors	6 (6.9)
Glucocorticoid dose	
0 mg/day	61 (70.1)
1–9 mg/day	18 (20.7)
≥10 mg/day	6 (6.9)
Missing/unknown	2 (2.3)
Disease activity	
Remission/low	69 (79.3)
Moderate/high	18 (20.7)
Confirmed COVID-19**	87 (100)
Vaccine	
Pfizer-BioNTech	45 (51.7)
Moderna	21 (24.1)
AstraZeneca/Oxford	6 (6.9)
Sinovac	5 (5.7)
Janssen/Johnson & Johnson	6 (6.9)
Don't know/missing	4 (4.6)

Continued

Table 1 Continued

Frequency (%) or mean (SD)

*Fully vaccinated: infection ≥ 14 days after second dose of a two-dose vaccine or first if Janssen/Johnson & Johnson.
 †Cases could have more than one disease diagnosis.
 ‡Other rheumatic diseases include mixed connective tissue (n=2), antiphospholipid antibody syndrome (n=1), autoinflammatory syndrome (n=1), IgG4-related disease (n=1), undifferentiated connective tissue disease (n=1), Still's disease (n=1) and palindromic rheumatism (n=1).
 §csDMARD medications included antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, ciclosporin, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine and tacrolimus; b/tsDMARD included abatacept, belimumab, CD20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, anti-TNF and Janus kinase inhibitors.
 ¶Other biologics include abatacept (n=4), IL-6 (n=2), IL-1 (n=2), belimumab (n=1) and ustekinumab (n=1).
 **Confirmed COVID-19 diagnosis: diagnosis made via PCR, antigen or antibody test.
 ††
 BMI, body mass index; b/tsDMARD, biologic/targeted synthetic disease-modifying antirheumatic drugs; C19-GRA, COVID-19 Global Rheumatology Alliance; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DMARD, disease-modifying antirheumatic drugs; JAK, Janus kinase; TNF, tumor necrosis factor.

glucocorticoids, 21% were taking prednisone 1–9 mg/day and 7% were on ≥ 10 mg/day. The majority (79%) had physician-reported remission or low disease activity at the time of breakthrough infection; 21% had moderate or high disease activity. The most common comorbidities were hypertension (28%), obesity (21%), lung disease (18%) and diabetes (10%); 47% had one or more comorbidities. The majority received messenger RNA (mRNA) vaccines (Pfizer n=45, 52%; Moderna n=21, 24%).

Among the fully vaccinated, infection occurred at a mean of 112 (± 60 , range 14–300) days after the second dose (figure 1) and 26% were hospitalised. The most common COVID-19 symptoms were cough (69%), fever (58%), malaise (52%), myalgia (39%) and shortness of breath (37%) (table 2). There were relatively few COVID-19 complications reported: three patients experienced acute respiratory distress syndrome (4%), five had a concomitant or secondary infection (three with pneumonia, one secondary sinus infection, one acute kidney injury; 6%), three patients experienced sepsis (4%) and no patients had cytokine storm reported.

Medications at the time of COVID-19 diagnosis are reported in online supplemental table 2 for the full cohort (n=197), for the fully vaccinated (n=87) and for those hospitalised among the fully vaccinated (n=22). Among the fully vaccinated, 24% were on methotrexate, compared with 9% of those who were both fully vaccinated and hospitalised. A similar pattern was seen for tumor necrosis factor (TNF) inhibitors (22% fully vaccinated vs 9% fully vaccinated and hospitalised). In contrast, 18% of those fully vaccinated were on BCDT, compared with 46% of those fully vaccinated

and hospitalised. Among the fully vaccinated and among the fully vaccinated and hospitalised, the majority were not taking systemic glucocorticoids at the time of vaccination (72% and 64%, respectively).

Among 79 fully vaccinated individuals with information on medication status at the time of vaccination, all but seven continued their antirheumatic medications before their vaccine doses (online supplemental table 3). Five discontinued medications after their vaccine doses. Otherwise medications were similar to those at the time of COVID-19 diagnosis.

Of those who were considered fully vaccinated, 22 were hospitalised (table 3). At the time of diagnosis, nine were being treated with BCDT, six as monotherapy and three in combination with other immunosuppressive medications. Three were on mycophenolate and three were on azathioprine. Among 17 individuals who had information on holding medications at the time of vaccination, only one individual withheld medications. Eleven received the Pfizer vaccine, five received Moderna, and two each received Janssen/Johnson & Johnson and Oxford/AstraZeneca. The median time from vaccination to COVID-19 diagnosis was 59 days (range 14–180 days). The four patients who required invasive ventilation subsequently died, and one patient who received non-invasive ventilation also died. Among the five deaths, one individual was aged 41–50, three individuals were aged 61–70 and one was over 80 years. Three individuals who died were on BCDT at the time of vaccination.

DISCUSSION

We found that over half of fully vaccinated individuals with rheumatic disease with breakthrough SARS-CoV-2 infections requiring hospitalisation had been taking either BCDT or mycophenolate at the time of COVID-19 diagnosis. Furthermore, we did not find any meaningful differences by hospitalisation status in glucocorticoid use among those with breakthrough infections. Reassuringly, breakthrough infections leading to hospitalisation were infrequent among those using other immunomodulators, including TNF inhibitors, corroborating findings from multiple registries.¹⁸

Despite the demonstrated efficacy of COVID-19 vaccines, particularly mRNA platform vaccines, breakthrough infections occurred in the fully vaccinated even prior to the emergence of more transmissible variants of concern.^{1–3} Cook *et al*¹⁶ reported a case series of 16 patients with rheumatic disease with breakthrough infections from a single healthcare system in Massachusetts, of whom 6 were hospitalised and 2 died. In the EULAR registries of breakthrough infections in patients with rheumatic disease, 28 individuals were fully vaccinated; 74% fully recovered while 2 died.¹⁵ A limitation of both our study and prior studies is the inability to confirm denominators for these populations of interest and thus we cannot estimate the incidence of SARS-CoV-2 infection following vaccination.

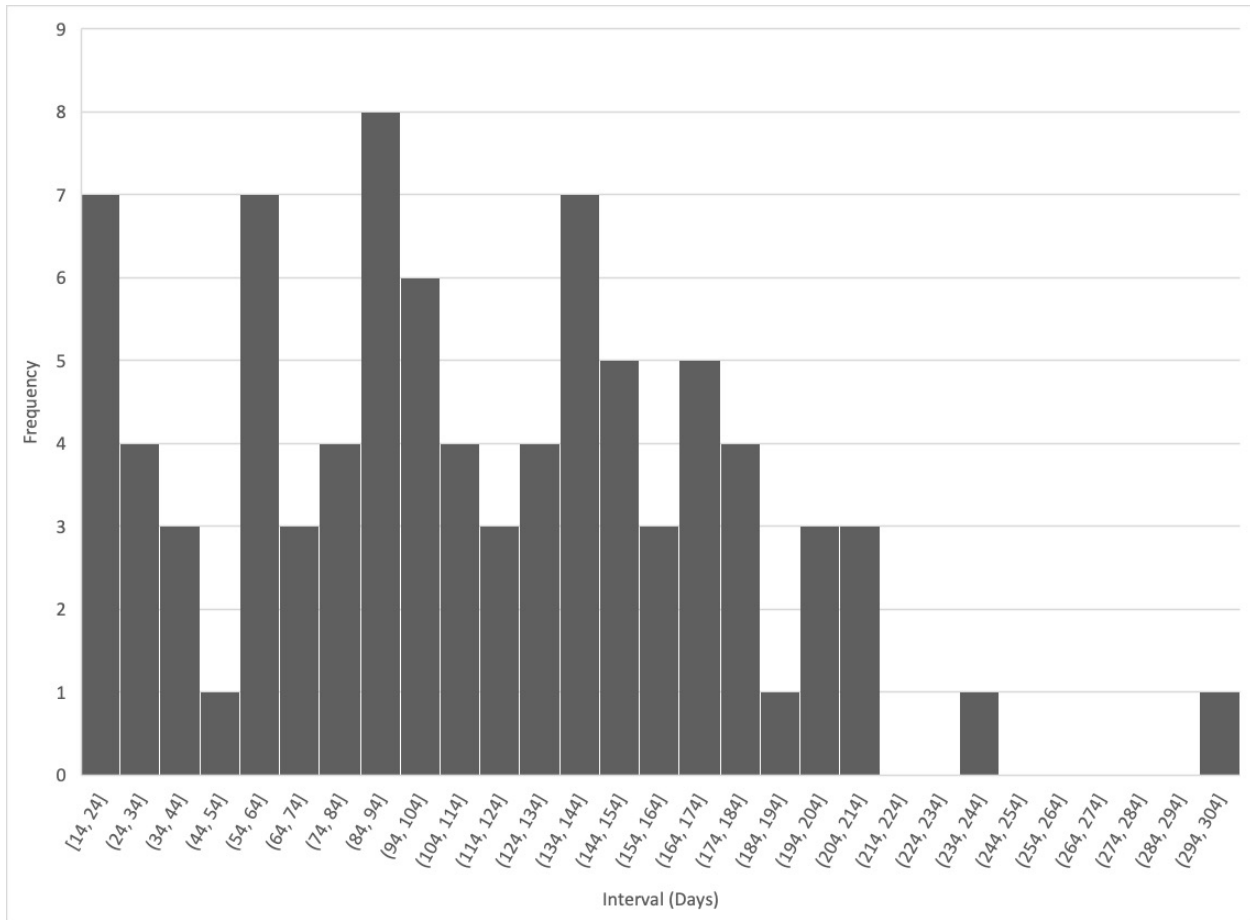


Figure 1 Number of days between last vaccination and SARS-CoV-2 infection among fully vaccinated individuals in the COVID-19 Global Rheumatology Alliance registry. The x-axis represents the interval of days during which infection occurred after the final dose of vaccine.

Table 2 COVID-19 symptoms and outcomes in fully vaccinated individuals with rheumatic disease who were vaccinated reported to the C19-GRA registry

Most frequent reported symptoms	n (%)
Cough	60 (69.0)
Fever	50 (57.5)
Malaise	45 (51.7)
Myalgia	34 (39.1)
Shortness of breath	32 (36.8)
COVID-19 complications	
ARDS	3 (3.5)
Sepsis	3 (3.5)
Concomitant or secondary infection	5 (5.8)
Cytokine storm (or MAS)	0 (0)
Outcomes	
Hospitalised (n=86*)	22 (26)
Death	5 (6)

*1 unknown status.

ARDS, acute respiratory distress syndrome; C19-GRA, COVID-19 Global Rheumatology Alliance; MAS, macrophage activation syndrome.

The impact on vaccine immunogenicity from medications used for rheumatic disease has been studied using surrogates for protection for humoral and T cell-mediated responses. In the general population, antibody neutralisation titres have correlated well with clinical protection against COVID-19.¹⁹ Overall, antibody titres have been lower among those with rheumatic disease and on immunosuppressive or immunomodulatory medications compared with healthy controls, particularly for those on BCDT such as rituximab or mycophenolate.^{4 5 20–28} In addition, several case series and cohort studies of people on rituximab showed that undetectable CD19-positive cells correlate with the lack of seroconversion, although this did not appear to affect the T cell response.^{6 19 20 25 29–32} The precise clinical implications of these lower antibody responses in conjunction with maintained T cell responses are still unclear.

Clinical data documenting the characteristics of rheumatology patients with breakthrough severe COVID-19 have been limited. In our study, 9 out of 22 fully vaccinated individuals hospitalised for breakthrough infections were treated with BCDT (41%), compared with 11% of individuals with infections after partial or full vaccination overall and 4% of the entire GRA registry as of 30 September 2021. Monotherapy or combination

Table 3 Details of fully vaccinated and hospitalised individuals reported to the C19-GRA registry (n=22)

Age and sex	Comorbidities	Rheumatic disease	Medications at the time of vaccination	Medications held for vaccination	Medications at the time of COVID-19 diagnosis	Vaccine received, time from last vaccination to SARS-CoV-2 infection	Outcome of hospitalisation*
31–40, F	None	Sjogren's	Hydroxychloroquine, methotrexate, BCDT	Unknown, B cell depletion unknown	Hydroxychloroquine, methotrexate, BCDT	Pfizer-BioNTech, 61 days	No supplemental oxygen
31–40, F	Lung disease, diabetes, chronic neurological/neuromuscular disease	SLE	Belimumab, mycophenolate	No	Belimumab, mycophenolate	Moderna, 23 days	No supplemental oxygen
31–40, F	Hypertension, BMI ≥30	Inflammatory myopathy	Leflunomide, BCDT, glucocorticoid	No, not B cell-depleted	Leflunomide, BCDT, glucocorticoid	Unknown, 30 days	Supplemental oxygen
31–40, F	None	Psoriatic arthritis	None	–	TNFi	Pfizer-BioNTech, 170 days	No supplemental oxygen
41–50, M	Hypertension	Psoriatic arthritis	None	–	None	Janssen/Johnson & Johnson, 24 days	Supplemental oxygen
41–50, F	Lung disease	RA	Azathioprine	Unknown	Azathioprine	Pfizer-BioNTech, 55 days	Supplemental oxygen
41–50, F	Lung disease, BMI ≥30, kidney disease	RA	Hydroxychloroquine, glucocorticoid	No	TNFi, hydroxychloroquine, glucocorticoid	Unknown, 120 days	Invasive ventilation/ECMO, death
41–50, F	Hypertension, kidney disease, organ transplant recipient, immunodeficiency, BMI >30	SLE	Mycophenolate, glucocorticoid	No	Mycophenolate, glucocorticoid	Pfizer-BioNTech, 14 days	Supplemental oxygen
51–60, F	Hypertension	RA	IL-6 inhibitor	Unknown	IL-6 inhibitor	AstraZeneca/Oxford, 30 days	Supplemental oxygen
61–70, M	Diabetes	Inflammatory myopathy	Glucocorticoid	No	BCDT, glucocorticoid	Pfizer-BioNTech, 180 days	Invasive ventilation/ECMO, death
61–70, M	Lung disease, hypertension, cardiovascular disease	Axial spondyloarthritis	BCDT	B cell-depleted	BCDT	Pfizer-BioNTech, 57 days	Non-invasive ventilation or high-flow oxygen devices, death

Continued

Table 3 Continued

Age and sex	Comorbidities	Rheumatic disease	Medications at the time of vaccination	Medications held for vaccination	Medications at the time of COVID-19 diagnosis	Vaccine received, time from last SARS-CoV-2 infection	Outcome of hospitalisation*
61–70, M	Lung disease, hypertension, cardiovascular disease, kidney disease	ANCA-associated vasculitis	BCDT	<i>B cell-depleted</i>	BCDT	Moderna, 14 days	Supplemental oxygen
61–70, F	Lung disease	RA	BCDT, glucocorticoid	GC: no, <i>B cell-depleted</i>	BCDT, glucocorticoid	Moderna, 78 days	Invasive ventilation, death
61–70, F	None	RA	Abatacept	No	Abatacept	AstraZeneca/Oxford, 65 days	Discharged from hospital (no ventilation reported)
61–70, F	Diabetes, BMI ≥ 30 , hypertension, cardiovascular disease, kidney disease	Vasculitis	Glucocorticoid	No	Glucocorticoid	Pfizer-BioNTech, 150 days	Supplemental oxygen
61–70, F	None	RA	None	–	Methotrexate, JAKi	Pfizer-BioNTech, 54 days	Supplemental oxygen
61–70, F	None	Systemic sclerosis, inflammatory myopathy	Azathioprine/6-MP, BCDT	<i>B cell depletion unknown</i>	Azathioprine/6-MP, BCDT	Moderna, 16 days	Discharged from hospital (no ventilation reported)
71–80, M	Hypertension, cardiovascular disease, kidney disease	Inflammatory myopathy	Mycophenolate	Unknown	Mycophenolate	Pfizer-BioNTech, 173 days	Supplemental oxygen
71–80, F	Lung disease	RA	BCDT	<i>B cell-depleted</i>	BCDT	Janssen/Johnson & Johnson, 38 days	Supplemental oxygen
>80, M	Lung disease, hypertension, cardiovascular disease	Vasculitis	BCDT, glucocorticoid	No, <i>B cell depletion unknown</i>	BCDT, glucocorticoid	Pfizer-BioNTech, 100 days	Invasive ventilation/ECMO, death
>80, M	Cardiovascular disease, cancer	Psoriatic arthritis	Glucocorticoid	Yes	Ustekinumab, glucocorticoid	Pfizer-BioNTech, 140 days	Non-invasive ventilation or high-flow oxygen devices

Continued

Table 3 Continued

Age and sex	Comorbidities	Rheumatic disease	Medications at the time of vaccination	Medications held for vaccination	Medications at the time of COVID-19 diagnosis	Vaccine received, time from last vaccination to SARS-CoV-2 infection	Outcome of hospitalisation*
>80, M	Hypertension, kidney disease	Vasculitis	BCDT	B cell depletion unknown	BCDT	Moderna, 180 days	Non-invasive ventilation or high-flow oxygen devices

*Highest level of hospital treatment; if no discharge status, they were alive at discharge.

ANCA, Antineutrophil cytoplasmic antibody; BCDT, B cell-depleting therapy; BMI, body mass index; C19-GRA, COVID-19 Global Rheumatology Alliance; ECMO, extracorporeal membrane oxygenation; F, female; GC, glucocorticoid; IL, interleukin; JAKi, Janus kinase inhibitor; M, male; 6-MP, 6-mercaptopurine; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNFi, tumor necrosis factor inhibitor.

therapy with mycophenolate was also over-represented among those hospitalised for breakthrough infections, although less frequently than BCDT. Reassuringly, cases of hospitalisation were infrequent in patients taking commonly prescribed medications like methotrexate and TNF inhibitors. Thus our findings, with real-world clinical outcomes, support the inferences drawn from prior studies that have used surrogates for protection.

There is a lack of data regarding comparative effectiveness between vaccine types in this population. In a cohort study of responses to Janssen/Johnson & Johnson versus mRNA vaccines among individuals with rheumatic disease, there were lower odds of seroconversion with the former.³³ Due to the nature of our study design and small numbers, we were unable to directly compare the efficacy of specific vaccines in the rheumatic disease population.

Due to concerns of lower efficacy of vaccination among the immunocompromised, additional doses of vaccine (typically third doses of an mRNA vaccine) have been studied among organ transplant recipients and haemodialysis patients and found to be safe and effective in increasing antibody levels.³⁴⁻³⁸ Improved humoral responses following a third vaccine dose have also been reported in people with rheumatoid arthritis^{39,40} and in a case series of 18 individuals with rheumatic disease.⁴¹ Multiple countries approved additional vaccine doses in the immunocompromised, including the UK in July and the USA in August 2021, before these were approved for the general population.⁷ While our study does not include data on breakthrough infection after an additional or third dose, the overall evidence has suggested that an additional dose is especially warranted in high-risk patients on certain immunosuppressive or immunomodulatory medications. Further studies reporting breakthrough infections in those with a third or fourth vaccine dose will help inform the effectiveness of this strategy.

The current totality of evidence^{4 5 20-25} supports the need to improve monoclonal antibody access^{42 43} for the most vulnerable patients who may not mount an adequate response following vaccination. In addition, further studies about passive immunity or pre-exposure prophylaxis are needed. Finally, new oral antiviral therapies may be potential options for administration in an outpatient setting, but more research on efficacy in people with rheumatic diseases or immunosuppressed populations is needed.^{44 45}

The strengths of this study include using a large global registry to collect data on breakthrough infections among people with rheumatic disease who have been vaccinated. However, limitations of our study must be acknowledged. First, there is potential for selection bias in this voluntary registry, particularly over-representation of those at highest risk of poor vaccine responses and thus breakthrough infections. Incidence rates, including mortality rates, cannot be reliably estimated using these data due to the lack of clear denominators for this population. Second, this study was cross-sectional, and although we assessed the timing of infection and medication holding with respect to the timing of vaccine doses, our study did not include biospecimen

collection to measure antibody titres or other surrogate measures of protection. Finally, although this case series is relatively large, the study design and small numbers within categories preclude assessing differences between rheumatic diseases, medication classes and vaccine types. We intentionally present descriptive data due to the lack of clear denominators and comparator group; as outlined in a recent paper, descriptive work is often harmed by inappropriate statistical adjustment or other statistical testing.⁴⁶ Given the descriptive nature of this work and the potential sources of bias, results should be interpreted with caution and studies with appropriate denominators (eg, prospective cohort studies) are necessary to confirm our results.

CONCLUSION

We present the largest series to date of breakthrough COVID-19 among people with rheumatic disease. Our data support prior findings of reduced vaccine immunogenicity based on the use of certain classes of anti-rheumatic medications. Given the high frequency of people with rheumatic disease on medications such as BCDT and mycophenolate who required hospitalisation, these patients should be prioritised and strongly recommended for other risk mitigation measures beyond additional doses of vaccine. Moreover, the current evidence supports the use of strategies that compensate for a reduced or absent humoral immune response to vaccination in high-risk individuals with rheumatic diseases, such as additional vaccine doses or pre-exposure or postexposure prophylaxis with monoclonal antibodies.

Author affiliations

- ¹Medicine, Section of Rheumatology, Boston University, Boston, Massachusetts, USA
- ²Department of Medicine, Division of Rheumatology, University of California, San Francisco, San Francisco, California, USA
- ³LupusChat, New York, New York, USA
- ⁴Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA
- ⁵Division of Rheumatology, Department of Medicine, University of California, San Francisco, San Francisco, California, USA
- ⁶Centre for Genetics and Genomics Versus Arthritis, The University of Manchester, Manchester, UK
- ⁷National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester, UK
- ⁸Division of Rheumatology, Department of Medicine, University of California, San Francisco, California, USA
- ⁹University of Manchester, Manchester, UK
- ¹⁰INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, INSERM, Sorbonne Université, Paris, France
- ¹¹APHU, Rheumatology Department, Hôpital Universitaire Pitie Salpêtrière, Paris, France
- ¹²Forschungsbereich Epidemiologie, Deutsches Rheuma-Forschungszentrum Berlin, Berlin, Germany
- ¹³Instituto de Salud Musculoesquelética (INMUSC), Madrid, Spain
- ¹⁴Epidemiology and Health Services Research, German Rheumatism Research Center Berlin, Berlin, Germany
- ¹⁵Portuguese League Against Rheumatic Diseases (LPCDR), Lisbon, Portugal
- ¹⁶Paul Stradins Clinical University Hospital, Riga, Latvia
- ¹⁷Blackrock Clinic, Blackrock, Ireland
- ¹⁸Gazi University, Ankara, Turkey
- ¹⁹Royal Hampshire County Hospital, Winchester, UK

- ²⁰Department of Internal Medicine, Hacettepe University, Ankara, Turkey
- ²¹Hacettepe University, Ankara, Turkey
- ²²Hamad Medical Corporation, Doha, Qatar
- ²³Rheumatology, Massachusetts General Hospital, Boston, Massachusetts, USA
- ²⁴Jaber Al Ahmed Al Jaber Al Sabah Hospital, Surra, Kuwait
- ²⁵University of Ghana Medical School, Accra, Ghana
- ²⁶Korle Bu Teaching Hospital, Accra, Ghana
- ²⁷Makati Medical Center, Makati City, Philippines
- ²⁸Rheumatology Associates Louisville, Louisville, Kentucky, USA
- ²⁹Inflammation and Immunity, Brigham and Women's Hospital, Boston, Massachusetts, USA
- ³⁰Rheumatology, Hospital Central "Dr Ignacio Morones Prieto", San Luis Potosí, Mexico
- ³¹Faculty of Medicine, Universidad Autónoma de San Luis Potosí, San Luis, Mexico
- ³²Massachusetts General Hospital, Boston, Massachusetts, USA
- ³³Autonomous University of Chihuahua, Chihuahua, Mexico
- ³⁴University of the Philippines Manila, Manila, Philippines
- ³⁵University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA
- ³⁶Asheville Arthritis & Osteoporosis Center, Asheville, North Carolina, USA
- ³⁷Cape Fear Arthritis Care, Leland, North Carolina, USA
- ³⁸Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, Massachusetts, USA
- ³⁹Department of Internal Medicine, Division of Rheumatology, University of Southern California, Los Angeles, California, USA
- ⁴⁰Crystal Run Healthcare, Middletown, New York, USA
- ⁴¹Lupus Foundation of America, Washington, DC, USA
- ⁴²Department of Medicine, University of Otago, Wellington, Wellington, New Zealand
- ⁴³University Of Otago, Wellington, New Zealand
- ⁴⁴Rheumatology, Boston Children's Hospital, Boston, Massachusetts, USA
- ⁴⁵Division of Rheumatology and Clinical Immunology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
- ⁴⁶Medicine, McMaster University, Hamilton, Ontario, Canada
- ⁴⁷Healthpartners, St Paul, Minnesota, USA
- ⁴⁸Harvard Medical School, Boston, Massachusetts, USA
- ⁴⁹MRC Centre for Neuromuscular Diseases, University College London, London, UK
- ⁵⁰Rheumatology, University College London Centre for Rheumatology, London, UK
- ⁵¹Faculty of Medicine, The University of Queensland, Herston, Queensland, Australia
- ⁵²Metro North Hospital and Health Service, Royal Brisbane and Women's Hospital Health Service District, Herston, Queensland, Australia
- ⁵³Medicine/Rheumatology, University of California, San Francisco, California, USA

Twitter Jean Liew @rheum_cat, Loreto Carmona @carmona_loreto, Pedro M Machado @pedromcmachado and Philip C Robinson @philiprobson

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ORCID iDs

Jean Liew <http://orcid.org/0000-0002-8104-2450>

Zara Izadi <http://orcid.org/0000-0002-1867-0905>

Saskia Lawson-Tovey <http://orcid.org/0000-0002-8611-162X>

Laure Gossec <http://orcid.org/0000-0002-4528-310X>

Anja Strangfeld <http://orcid.org/0000-0002-6233-022X>

Loreto Carmona <http://orcid.org/0000-0002-4401-2551>

Martin Schäfer <http://orcid.org/0000-0001-6487-3634>

Gözde Kübra Yardımcı <http://orcid.org/0000-0001-9543-4685>

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

Jonathan Hausmann <http://orcid.org/0000-0003-0786-8788>

Emily Sirotych <http://orcid.org/0000-0002-7087-8543>

Pedro M Machado <http://orcid.org/0000-0002-8411-7972>

Philip C Robinson <http://orcid.org/0000-0002-3156-3418>

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