ORIGINAL RESEARCH

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

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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=14), 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
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-GRA registry (n=87)

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

*Continued*
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.

**Table 1**

<table>
<thead>
<tr>
<th>Frequency (%) or mean (SD)</th>
</tr>
</thead>
</table>

*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), autoimmune inflammatory 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/tar disease-modifying antirheumatic drugs; DMARD, disease-modifying antirheumatic drugs; C19-19, COVID-19 Global Rheumatology Alliance; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; GRA, COVID-19 vaccine doses; mRNA, messenger RNA vaccines; Pfizer n=45, 52%; Moderna n=21, 24%.

**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.16,19 Cook et al16 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.
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. 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. 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. 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)

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

Continued
<table>
<thead>
<tr>
<th>Age and sex</th>
<th>Comorbidities</th>
<th>Rheumatic disease</th>
<th>Medications at the time of vaccination</th>
<th>Medications held for vaccination</th>
<th>Medications at the time of COVID-19 diagnosis</th>
<th>Vaccine received, time from last vaccination to SARS-CoV-2 infection</th>
<th>Outcome of hospitalisation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>61–70, M</td>
<td>Lung disease, hypertension, cardiovascular disease, kidney disease</td>
<td>ANCA-associated vasculitis</td>
<td>B cell-depleted</td>
<td>BCDT</td>
<td>Moderna, 14 days</td>
<td>Supplemental oxygen</td>
<td></td>
</tr>
<tr>
<td>61–70, F</td>
<td>Lung disease</td>
<td>RA</td>
<td>BCDT, glucocorticoid</td>
<td>GC: no, B cell-depleted</td>
<td>BCDT, glucocorticoid</td>
<td>Moderna, 78 days</td>
<td></td>
</tr>
<tr>
<td>61–70, F</td>
<td>None</td>
<td>RA</td>
<td>Abatacept</td>
<td>No</td>
<td>Abatacept</td>
<td>AstraZeneca/Oxford, 65 days</td>
<td>Discharged from hospital (no ventilation reported)</td>
</tr>
<tr>
<td>61–70, F</td>
<td>Diabetes, BMI ≥30, hypertension, cardiovascular disease, kidney disease</td>
<td>Vasculitis</td>
<td>Glucocorticoid</td>
<td>No</td>
<td>Glucocorticoid</td>
<td>Pfizer-BioNTech, 150 days</td>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>61–70, F</td>
<td>None</td>
<td>RA</td>
<td>None</td>
<td>–</td>
<td>Methotrexate, JAKi</td>
<td>Pfizer-BioNTech, 54 days</td>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>61–70, F</td>
<td>None</td>
<td>Systemic sclerosis, inflammatory myopathy</td>
<td>Azathioprine/6-MP, BCDT</td>
<td>B cell depletion unknown</td>
<td>Azathioprine/6-MP, BCDT</td>
<td>Moderna, 16 days</td>
<td>Discharged from hospital (no ventilation reported)</td>
</tr>
<tr>
<td>71–80, M</td>
<td>Hypertension, cardiovascular disease, kidney disease</td>
<td>Inflammatory myopathy</td>
<td>Mycophenolate</td>
<td>Unknown</td>
<td>Mycophenolate</td>
<td>Pfizer-BioNTech, 173 days</td>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>71–80, F</td>
<td>Lung disease</td>
<td>RA</td>
<td>BCDT</td>
<td>B cell-depleted</td>
<td>BCDT</td>
<td>Janssen/Johnson &amp; Johnson, 38 days</td>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>&gt;80, M</td>
<td>Lung disease, hypertension, cardiovascular disease</td>
<td>Vasculitis</td>
<td>BCDT, glucocorticoid</td>
<td>No, B cell depletion unknown</td>
<td>BCDT, glucocorticoid</td>
<td>Pfizer-BioNTech, 100 days</td>
<td>Invasive ventilation/ECMO, death</td>
</tr>
<tr>
<td>&gt;80, M</td>
<td>Cardiovascular disease, cancer</td>
<td>Psoriatic arthritis</td>
<td>Glucocorticoid</td>
<td>Yes</td>
<td>Ustekinumab, glucocorticoid</td>
<td>Pfizer-BioNTech, 140 days</td>
<td>Non-invasive ventilation or high-flow oxygen devices</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
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. 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. Despite 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. Improved humoral responses following a third vaccine dose have also been reported in people with rheumatoid arthritis and in a case series of 18 individuals with rheumatic disease. 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. While our study does not include data on breakthrough infection after an additional or third dose, the overall evidence has suggested that an additional or third dose is especially efficacious in high-risk populations. Further studies reporting breakthrough infections in these with a third or fourth vaccine dose will help inform the effectiveness of this strategy. Understanding the factors that contribute to breakthrough infections among vaccine recipients is crucial for improving vaccination strategies in this vulnerable population.

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 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 vaccination, incidence rates, including mortality rates, cannot be reliably estimated using these data due to the lack of clear denominators for this population. Finally, the current totality of evidence supports the need to improve monoclonal antibody access for the most vulnerable patients who may not mount an adequate response following vaccination. In addition, further studies are needed to evaluate the role of passive immunity or pre-exposure prophylaxis in people with rheumatic diseases or immunosuppressed populations. Further studies about passive immunity or pre-exposure prophylaxis 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.

Table 3

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

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

Table 3 Continued
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. 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.

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Patient consent for publication Not required.

Ethics approval The C19-GRA physician registry was determined to be ‘not human subjects research’ under US federal guidelines as assessed by the University of California, San Francisco, and patient consent was therefore not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Researchers interested in performing additional analyses from survey data are invited to submit proposals through the COVID-19 Global Rheumatology Alliance at rheum-covid.org. For approved projects, we will be able to provide summary tables and data analyses as requested. We do not currently have IRB approval to make the raw data available to other researchers.

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