SARS-CoV-2 antibody response after COVID-19 in patients with rheumatic disease

The impacts of rheumatic disease and immunosuppression on the development of antibodies to SARS-CoV-2 are unknown. A study of healthcare workers showed that detectable SARS-CoV-2 antibodies were associated with reduced risk of SARS-CoV-2 reinfection, and the robustness of this neutralising antibody response has implications for seroprevalence studies and vaccine efficacy. While disease-modifying antirheumatic drugs (DMARDs) generally blunt the immune response to pathogens, immunosuppressive medications such as dexamethasone and baricitinib have efficacy in reducing the severity of COVID-19. Additionally, tumour necrosis factor inhibition has been proposed as a potential mechanism for enhancing germinal centre formation and antibody production in severe COVID-19. Understanding the SARS-CoV-2 antibody response after COVID-19 among rheumatic disease patients is therefore of particular interest.

We examined the SARS-CoV-2 antibody response among patients with rheumatic diseases and past COVID-19 at the Mass General Brigham (MGB) health system in Boston, Massachusetts, USA. Patients with COVID-19 confirmed by positive PCR testing and rheumatic disease confirmed by electronic health record (EHR) review were identified as previously described. We extracted clinically obtained SARS-CoV-2 antibody results and other relevant variables from the EHR. This study was considered exempt by the MGB Institutional Review Board.

Out of 188 patients with PCR-confirmed COVID-19 and rheumatic disease, 13 patients had subsequent SARS-CoV-2 antibody testing (table 1). Of these, 2 had undetectable antibodies, 1 had variable results and 10 had positive antibodies. Of the two patients with negative antibodies, one patient had psoriatic arthritis treated with leflunomide and prednisone and had an uncomplicated COVID-19 course. The other patient had antineutrophil cytoplasmic antibody-associated vasculitis on rituximab, azathioprine and prednisone. This patient had negative SARS-CoV-2 antibodies between 28 and 216 days after COVID-19 and had a complicated course requiring intensive care unit admission. One patient with antiphospholipid syndrome on prednisone, cyclophosphamide, rituximab and eculizumab had initial positive antibodies 28 to 87 days after
COVID-19. However, he had a negative antibody response by 107 days despite persistently positive PCR testing, phylogenetic analysis suggestive of persistent infection and viral evolution, and clinical concern for recurrent COVID-19, and he died from respiratory failure, as reported elsewhere.5

The remaining 10 patients had detectable SARS-CoV-2 antibodies despite the presence of rheumatic diseases and/or the use of immunosuppressive medications, including prednisone, methotrexate, azathioprine, etanercept, rituximab and belimumab. The median time between SARS-CoV-2 PCR and antibody testing was 91 days (IQR: 60–146 days). Of these 10 patients, 8 patients had full recovery, 1 patient had persistent fatigue, and 1 patient with systemic lupus erythematosus (without prior haematologic involvement) had a complicated course with recurrent episodes of thrombotic thrombocytopenic purpura.

This case series of rheumatic disease patients with PCR-confirmed COVID-19 and clinically obtained SARS-CoV-2 antibody testing indicates that the majority of patients (10, 77%) developed detectable SARS-CoV-2 antibodies, which is reassuring. Three patients had negative or variable SARS-CoV-2 antibodies, and two of these patients had severe COVID-19. Three patients were on rituximab; two patients on rituximab for many years had undetectable circulating CD19 + B cells and undetectable or variable SARS-CoV-2 antibodies, while one patient who had recently started rituximab (flow cytometry not available) had detectable SARS-CoV-2 antibodies. As tests were obtained as part of routine clinical care at a tertiary care centre, generalisability may be limited, antibody titers and tests for neutralising antibodies are not available, and the timing of antibody testing relative to SARS-CoV-2 infection is variable. Further studies are needed to investigate the effects of specific rheumatic diseases and DMARDS on the efficacy and durability of the antibody response to SARS-CoV-2.

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Table 1 SARS-CoV-2 antibody test results in rheumatic disease patients with COVID-19 confirmed by PCR

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Sex</th>
<th>Rheumatic disease diagnosis</th>
<th>Rheumatic disease treatment</th>
<th>Timing of SARS-CoV-2 antibody test(s) relative to first positive COVID-19 PCR</th>
<th>SARS-CoV-2 antibody test result(s)</th>
<th>COVID-19 complications</th>
<th>COVID-19 pharmacologic treatment</th>
<th>COVID-19 clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/variable SARS-CoV-2 antibodies</td>
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<tr>
<td>48 Female</td>
<td>Psoriatic arthritis</td>
<td>Leflunomide 10 mg daily, prednisone 10 mg daily</td>
<td>T+177 days</td>
<td>Negative total antibody* None None Fully recovered</td>
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<tr>
<td>62 Female</td>
<td>ANCA-associated vasculitis</td>
<td>Rituximab 1 g (started T−6 years, most recent dose T−149 days), azathioprine 100 mg daily, prednisone 7.5 mg daily</td>
<td>T+28 days T+71 days T+111 days T+216 days</td>
<td>Negative IgG, negative IgM Negative total antibody* Negative total antibody* Negative total antibody* Negative total antibody* Hospitalisation with ICU admission Respiratory failure requiring oxygen therapy by high flow nasal cannula Hydroxychloroquine, Remdesivir Persistent cough (T+238 days). Oxygen requirement resolved by hospital discharge</td>
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<tr>
<td>45 Male</td>
<td>Antiphospholipid syndrome</td>
<td>Prednisone 15 mg daily, cyclophosphamide 250 mg daily, rituximab 1 g (started T−5 years, most recent dose T−11 days), ecuclizumab 800 mg (started and most recent dose T−9 days)</td>
<td>T+28 days T+81 days T+107 days</td>
<td>Positive IgM, negative IgG Positive IgM, positive IgG‡ Positive IgM, positive IgG‡ Negative total antibody* Hospitalisation with ICU admission Respiratory failure requiring mechanical ventilation; circulatory shock Remdesivir, SARS-CoV-2 antibody cocktail (regeneron) (T+145 days) Death (T+154 days)</td>
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<tr>
<td>Positive SARS-CoV-2 antibodies</td>
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<tr>
<td>26 Female</td>
<td>Systemic lupus erythematosus</td>
<td>None</td>
<td>T+1 hour T+7 days</td>
<td>Positive total antibody* Positive total antibody* Hospitalisation with ICU admission TTP requiring plasma exchange and glucocorticoids None None Fully recovered</td>
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<tr>
<td>71 Female</td>
<td>Rheumatoid arthritis</td>
<td>None</td>
<td>T+58 days</td>
<td>Positive total antibody* None None Fully recovered</td>
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<tr>
<td>73 Male</td>
<td>Psoriatic arthritis</td>
<td>Etanercept 50 mg weekly</td>
<td>T+60 days</td>
<td>Positive total antibody* None None Fully recovered</td>
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<tr>
<td>54 Female</td>
<td>Systemic lupus erythematosus</td>
<td>Rituximab 720 mg (started T−86 days, most recent dose T−2 days)</td>
<td>T+60 days</td>
<td>IgG positive, IgM not performed None None Fully recovered</td>
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<tr>
<td>63 Female</td>
<td>Systemic lupus erythematosus</td>
<td>Azathioprine 100 mg daily, belimumab 220 mg monthly (started T−336 days, most recent dose T−20 days)</td>
<td>T+88 days</td>
<td>Positive total antibody* None None Fully recovered</td>
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<tr>
<td>55 Female</td>
<td>Sarcoidosis</td>
<td>None</td>
<td>T+93 days</td>
<td>Positive total antibody* None None Fully recovered</td>
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<tr>
<td>52 Female</td>
<td>Rheumatoid arthritis</td>
<td>None</td>
<td>T+94 days T+210 days</td>
<td>Positive total antibody* Positive total antibody* Hospitalisation without ICU admission Supplemental oxygen by nasal cannula None None Fully recovered</td>
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<tr>
<td>68 Female</td>
<td>Polyarthritis</td>
<td>Prednisone 6 mg daily, methotrexate 25 mg weekly</td>
<td>T+129 days</td>
<td>Positive total antibody* None None Fully recovered</td>
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<tr>
<td>51 Female</td>
<td>Neuromyelitis optica</td>
<td>Methotrexate 15 mg weekly</td>
<td>T+155 days</td>
<td>Positive total antibody* None None Fully recovered</td>
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<tr>
<td>72 Female</td>
<td>Psoriatic arthritis</td>
<td>Methotrexate 25 mg weekly</td>
<td>T+203 days</td>
<td>Positive total triobody* None None Fully recovered</td>
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</tbody>
</table>

*Measured with the Roche Elecsys assay, which reports the positivity of total SARS-CoV-2 antibody (IgM and IgG) and has 99.5% sensitivity at 14 days after COVID-19 infection.
†Measured with the Viracor Eurofins assay, which reports IgM and IgG antibody positivity to SARS-CoV-2. The sensitivity of the assay is unknown.
ANCA, antineutrophil cytoplasmic antibody; ICU, intensive care unit; PCR, polymerase chain reaction; T, time zero; TTP, thrombotic thrombocytopenic purpura.
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