


clinical pressures of the pandemic. Of the 65 patients included in the cohort, BVAS data were provided for 28 (43%), but this was not included in the analysis as the proportion of missing data was deemed too high.

Of the patients who died, 11 of 18 were deemed to be in remission by the treating clinician at the time of COVID-19 diagnosis, 5 of 18 had moderate disease activity, and 2 of 18 had minimal disease activity. The cause of death in all patients was deemed likely, or highly likely, to be attributable to COVID-19. Clinical information was incomplete for 1 patient; this patient's death was presumed to be attributable to COVID-19, and there was no mention of active vasculitis at any point in the case report form. In 1 other patient, active vasculitis was considered to be the possible cause of death, but on balance, COVID-19 was deemed the more likely cause.

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Rapid attenuation of anti-SARS-CoV-2 antibodies in patients with musculoskeletal diseases in whom intensive immunosuppressive therapies were reinitiated after COVID-19: comment on the article by Curtis et al

To the Editor:

We read with great interest the recently published, updated guidance from the American College of Rheumatology on COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases (RMDs) (1). Because the expected response to vaccination was deemed likely to be blunted in many RMD patients receiving treatment with certain systemic immunomodulatory therapies (2–4), interrupting or otherwise optimizing the timing of some immunomodulatory therapies was recommended. However, the impairment of long-term immunologic memory of SARS-CoV-2 (5) remains a concern in RMD patients requiring continuous immunomodulatory therapies after infection.

We recently assessed the longitudinal antibody response in patients with RMDs who experienced natural SARS-CoV-2 infection, and we report the results herein. Patients were infected with SARS-CoV-2 during a COVID-19 outbreak in the Daini Osaka Police Hospital in Japan. A post-COVID-19

monthly follow-up serosurvey was conducted using an anti-SARS-CoV-2 spike S1 protein and nucleocapsid protein immunoassay (Elecys; Roche) 2–11 months postinfection in 10 patients with RMDs (Table 1). The patients were receiving intensive immunomodulatory therapies prior to SARS-CoV-2 infection, and immunosuppressive therapy was reinitiated after recovery from the infection. The severity of COVID-19 was determined based on the World Health Organization Clinical Progression Scale (6). All patients exhibited a sufficient antibody response to SARS-CoV-2 at 2–3 months postinfection. The initial antibody response to the spike S1 protein was maintained until 9–11 months in most patients. Antibody retention in these patients was comparable to that reported in healthy individuals in previous studies (7,8).

However, the initial favorable spike S1 protein antibody titer decreased in 2 patients in whom intensive immunosuppressive therapies were reinitiated after COVID-19 (Table 1). One of the patients resumed cyclosporin A (CSA) therapy (Supplementary Figure 1A, available on the *Arthritis & Rheumatology* website at <https://onlinelibrary.wiley.com/doi/10.1002/art.42003>), and the other patient, who had thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO; a variant of multicentric Castleman's disease [8]), resumed weekly treatment with subcutaneous tocilizumab with CSA (Supplementary Figure 1B). Intensive immunosuppressive therapy, such as treatment with CSA, may alter immunologic memory that contributes to long-term protective immunity. Conversely, the spike S1 protein antibody response remained stable in a patient in whom intensive immunosuppressive therapy was suspended after COVID-19 infection (Supplementary Figure 1C).

This report presents the findings from a longitudinal serosurvey of natural SARS-CoV-2 infection in patients with RMDs who were receiving immunomodulatory therapies. In all patients, treatment with immunomodulatory therapy was withheld during infection and resumed after the patients recovered. At 9 months after infection with SARS-CoV-2, the serum retained <40% of the neutralizing antibodies arising from infection among those patients who continued to receive aggressive immunosuppressive therapy following the onset of COVID-19. The shorter-duration immunity conferred by natural SARS-CoV-2 infection in patients with RMDs receiving immunomodulatory therapies suggests that the estimated duration of vaccine-induced protection against COVID-19 might be shorter in these patients than in the general population, potentially necessitating reimmunization. A third dose of a COVID-19 vaccine is being considered for solid organ transplant recipients who are receiving immunosuppressive therapy (9,10). Further large-scale studies are warranted to confirm the influence of immunomodulatory therapies on the maintenance of immunity against COVID-19.

Table 1. Response to anti-SARS-CoV-2 antibodies and immunosuppressant treatment in patients with AIIRD and COVID-19*

Disease	Age/ sex	Immunosuppressants		Severity of COVID-19 (WHO Clinical Progression Scale score)	Anti-spike S1 antibody		Antinucleocapsid antibody	
		Pre-COVID-19	Post-COVID-19		Response	Retention rate, %	Response	Retention rate, %
SSc; ILD; PAH	53/M	Prednisolone 12.5 mg; CSA 150 mg; IV CYC 1,000 mg	Prednisolone <15 mg; CSA 200-250 mg	Severe (7)	High	9.6	Low	10.7
SSc; SS; PAH	54/F	Prednisolone 10 mg; AZA 100 mg	Prednisolone <10 mg; AZA 100 mg	Severe (7)	High	98.3	Middle	64.3
PMR	75/F	Prednisolone 10 mg	Prednisolone <15 mg	Severe (7)	High	96.0	Low	50.0
PM; ILD	76/M	Prednisolone 25 mg; tacrolimus 1 mg	Prednisolone <10 mg; tacrolimus 1 mg	Moderate (5)	High	100.0	High	58.9
MPA	75/M	Prednisolone 12 mg; IV CYC 800 mg	Prednisolone <15 mg; AZA 100 mg	Moderate (5)	High	100.0	High	44.5
TAFRO	59/M	Prednisolone 35 mg; CSA 150 mg; SC TCZ 162 mg every week	Prednisolone <30 mg; CSA 50-100 mg; SC TCZ 162 mg every week	Mild (1)	High	36.4	High	12.2
RA	63/F	MTX 4 mg/week	None	Mild (2)	High	100.0	High	25.2
RA; ILD	76/F	Prednisolone 10 mg	Prednisolone <10 mg	Mild (2)	High	NA	Low	NA
SpA	48/F	Balicitinib 4 mg; MTX 8 mg/week	Balicitinib 4 mg; MTX 8 mg/week	Mild (2)	Low	NA	Low	NA
RA	32/F	CZP 200 mg every 2 weeks; MTX 8 mg/week; prednisolone 5 mg	CZP 200 mg every 2 weeks; MTX 8 mg/week; prednisolone <5 mg	Mild (2)	Low	NA	Low	NA

* The severity of COVID-19 was determined based on the World Health Organization Clinical Progression Scale (maximum WHO Clinical Progression Scale Score) (6). Antibodies were measured using an anti-SARS-CoV-2 spike S1 protein and nucleocapsid protein assay (Eitest; Roche). The antibody retention rate was determined by dividing the patient's antibody titer at 9-11 months by the maximum antibody titer. Antibody response category is based on the maximum antibody titer for each patient. Anti-spike S1 antibody levels were classified as high (>200 units/ml), moderate (>60 units/ml), or low (<60 units/ml). Antinucleocapsid antibody levels were classified as high (cutoff index [COI] >60), moderate (COI >20), or low (COI <60). AIIRD = autoimmune inflammatory rheumatic disease; SSc = systemic sclerosis; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; CSA = cyclosporin A; IV = intravenous; CYC = cyclophosphamide; SS = Sjögren's syndrome; AZA = azathioprine; PMR = polymyalgia rheumatica; PM = polymyositis; MPA = microscopic polyangiitis; TAFRO = thrombocytopenia, anasarca, fever, reticulocytosis, organomegaly; SC = subcutaneous; TCZ = tocilizumab; RA = rheumatoid arthritis; MTX = methotrexate; NA = data not available; SpA = spondyloarthritis; CZP = certolizumab pegol.

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Risk of nonserious infections in rheumatoid arthritis: comment on the article by Bechman et al

To the Editor:

We read with interest the article by Dr. Bechman and colleagues in which they reported that nonserious infections occur frequently in patients with rheumatoid arthritis (1). As experts in respiratory viral infections, we see some problems with their study.

The definition of “nonserious infection” is diffuse and too heterogeneous. Dr. Bechman and colleagues use the term to refer to a wide range of bacterial and viral infections, including opportunistic herpes zoster and fungal infections. Upper respiratory tract viral infections (the common cold) were not obviously included in the study. Acute respiratory infection is the most common acute illness in humans, accounting for 43% of the total burden of diseases (2). A recent study including 204 countries indicated that the incidence of the common cold was 2.25 episodes per individual per year (2). This incidence is consistent with that found in several earlier studies (3–5). The common cold is not a nonsignificant nonserious infection. The mean duration of symptoms is 10 days, and symptoms may significantly impair life quality and productivity (2,6).

In the 3-year study conducted by Dr. Bechman and colleagues, the information was collected using questionnaires that were returned every 6 months. For reliable information, weekly online symptom diaries or internet-based syndrome monitoring should have been used (4,5). The questionnaire items were not specified, and we wonder whether questions regarding acute onset of sore throat, rhinorrhea, nasal congestion, and cough (common cold) were included (6). The authors asked details only about new prescriptions (including antibiotics) and hospital attendance. With these limited questions the data collection was selective. Only 63% of patients returned more than two-thirds of the required diaries, which weakens the generalization of the observations.

The authors state that they demonstrated a high frequency of nonserious infections in patients with rheumatoid arthritis. For every 100 patients, they reported a rate of 14 nonserious respiratory and ear, nose, and throat infections per year, meaning that 86 of 100 patients annually experienced no respiratory infections. This observation is hard to believe, given that the mean annual incidence of acute respiratory illness in adults is 1–4 (2–5).

We think that the uncontrolled study by Dr. Bechman and colleagues does not reliably answer the question of the risk of nonserious infections in patients with rheumatoid arthritis. It only reliably compares the occurrence of the specific illnesses asked about between different treatment groups.