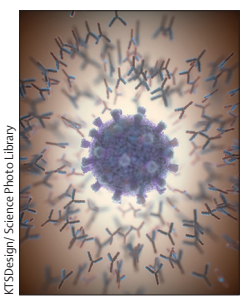
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 in patients with rheumatic disease: finally, a denominator



KTSDesign/ Science Photo Library

Published Online
April 28, 2021
https://doi.org/10.1016/S2665-9913(21)00121-1

See Articles page e481

When the pandemic arrived in early 2020, rheumatology received more attention than many other medical subspecialities. There was a tremendous amount of interest in whether hydroxychloroquine was preventive or ameliorative, along with controversy over whether patients with autoimmune disease or those who were immunocompromised were more or less likely to become infected, and increasing reports of rheumatic syndromes appearing among patients with COVID-19, including coagulopathies, cytokine storm syndromes, multisystem inflammatory syndrome in children and adults, and vasculopathies presenting with features of chilblains or Raynaud's phenomenon. Ultimately, agents used to manage patients with rheumatic diseases, such as tocilizumab, dexamethasone, and baricitinib, were found to be beneficial for pulmonary and other complications of severe COVID-19.[1] More recently, guidance documents have attempted to clarify the role for vaccinations in immune-compromised patients, especially those on anti-inflammatory agents.[2] Rheumatologists' proactive response in developing global research collaborations has created new opportunities. For example, the COVID-19 Global Rheumatology Alliance started a registry that began to enrol patients with rheumatic diseases infected with SARS-CoV-2 within the first weeks of the pandemic.[3]

Ultimately, nearly a year elapsed before two of the most important outstanding questions were meaningfully addressed: whether patients with rheumatic disease are more or less likely to become infected with SARS-CoV-2, and whether the severity of illness in these patients was different to that in the public at large. In other words, after hearing about many cases, we finally have a denominator so comparisons can be made. In *The Lancet Rheumatology*, David Saadoun and colleagues present a multicentre study[4] of 3028 patients with rheumatoid arthritis, axial spondyloarthritis, systemic lupus erythematosus, Sjogren's syndrome, and giant cell arteritis, from six referral centres in Europe (France, Germany, Italy, Portugal, Spain, and the UK). Patients were derived from well described and well characterised cohorts, and the results are of great interest. The reported prevalence of SARS-CoV-2 antibodies, hospital admissions, and deaths were the same as in the general population. 519 (20·6%) of 2514 patients had treatment changes, of which 125 (24·1%) were due to the pandemic, and a 654 (21·6%) of 3028 patients had at least one disease flare—a proportion that is probably not dissimilar to that seen in normal times. C-reactive protein was found to be a reliable marker of symptomatic COVID-19 (odds ratio 1·18, 95% CI 1·05–1·33; p=0·0063).

However, the study had many limitations. The reported SARS-CoV-2 seropositivity rates were relatively low (eg, several states in the USA had rates that were several times higher), patients in the study were usually only tested on one occasion, and there were too few hospital admissions or fatal events to generate any real conclusions. Racial and ethnic diversity among the patients followed up is also likely to have been limited as established European rheumatology cohorts are overwhelmingly white.

More than 110 000 articles on COVID-19 have appeared in the peer-reviewed literature, but fewer than 1% of them involve patients with autoimmune disorders. As such, the impact of published data from patients with autoimmune diseases largely remains unclear, and many questions remain. Since patients with systemic lupus erythematosus have higher levels of type I interferon, might this minimise the severity of COVID-19? Calabrese and colleagues[5] raised the concern that anti-interferon agents might be less protective of certain infections and are associated with a relative high prevalence of herpesvirus infections. Patients with severe COVID-19 have also been found to harbour 40 times more autoantibodies against type 1 interferon than healthy individuals.[6] As such, it is possible that the immunomodulating agents taken by patients with autoimmune rheumatic diseases might affect the course of COVID-19. And what can cytokine storm syndromes in COVID-19 teach us about managing rheumatic conditions in which vasculitis and complement activation are evident? The timing of therapy in COVID-19 is undoubtedly crucial, but outstanding questions include whether interleukin-6 and Janus kinase 1 inhibition should be used earlier, and what the optimal timing of antiplatelet and anticoagulant therapies should be. It is also unclear why patients with

vasculitis or spondyloarthropathies have similar outcomes as the general population when they develop COVID-19. Finally, whether the reported appearance of new-onset IgG autoantibodies in patients admitted to hospital with COVID-19 is an epiphenomenon or is of physiological importance also remains unknown.[7]

Many of us remember highly publicised post-viral fatigue syndromes described in the 1980s (eg, so-called yuppie flu resulting from Epstein-Barr virus infection). Long COVID-19 appears to have a similar presentation but is associated with the appearance of nerve tissue-associated autoantibodies.[8] Unfortunately, there has been no research on this phenomenon in patients with rheumatic diseases. Many of the patients with rheumatic diseases treated at our centre had transient flares after receiving COVID-19 vaccination, but the peer-reviewed literature has so far been largely silent on this subject. As tragic as the pandemic has been, basic insights into the inflammatory process will evolve and help us to better manage our patients with rheumatic disease. There is a considerable space for investigation in these important areas.

I declare no competing interests.

Daniel J Wallace
daniel.wallace@cshs.org

Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

1 Calabrese L, Winthrop KL. Rheumatology and COVID-19 at 1 year: facing the unknowns. *Ann Rheum Dis* 2021; published online March 3. https://doi.org/10.1136/annrheumdis-2021-219957.
2 ACR COVID-19 Vaccine Clinical Guidance Task Force. COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases. March 4, 2021. https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf (accessed April 20, 2021).
3 Robinson RP, Yazdany J, Machado PM. Global research collaboration in a pandemic-challenges and opportunities: the COVID-19 Global Rheumatology Alliance. *Curr Opin Rheumatol* 2021; **33:** 111–16.
4 Saadoun D, Vieira M, Vautier M, et al. SARS-CoV-2 outbreak in immune-mediated inflammatory diseases: the Euro-COVIMID multicentre cross-sectional study. *Lancet Rheumatol* 2021; published online April 28. https://doi.org/10.1016/S2665-9913(21)00112-0.
5 Calabrese LH, Winthrop K, Strand V, Yazdany, Walter JE. Type 1 interferon, anti-interferon antibodies and COVID-19. *Lancet Rheumatol* 2021; **3:** e246–47.
6 Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; **370:** eabd4585.
7 Cheng SE, Feng A, Meng W, et al. New-Onset IgG autoantibodies in hospitalized patients with COVID-19. *medRxiv* 2021; published online Jan 29. https://doi.org/10.1101/2021.01.27.21250559 (preprint).
8 Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *medRxiv* 2020; published online Dec 19. https://doi.org/10.1101/2020.12.10.20247205 (preprint).

Rituximab for the treatment of systemic sclerosis: urgent need for an international randomised controlled trial

Published **Online** May 26, 2021 https://doi.org/10.1016/S2665-9913(21)00149-1

See **Articles** page e489

Systemic sclerosis is a complex disease characterised by autoimmunity, widespread tissue fibrosis, and vascular abnormalities; however, the underlying pathobiology remains incompletely understood.[1] Despite major advances in the management of the disease including a wide therapeutic armamentarium, systemic sclerosis is still associated with substantial morbidity and mortality.[1] B cells have been strongly implicated in the pathogenesis of systemic sclerosis with evidence including tissue infiltration (eg, skin and lung) and the production of specific systemic sclerosis-associated autoantibodies.[2] Rituximab is a monoclonal chimeric antibody against CD20 that depletes peripheral B cells and has been investigated in systemic sclerosis. Rituximab has been reported to have beneficial effects on skin fibrosis and lung fibrosis; however, the evidence base to date is scant.[2]

In *The Lancet Rheumatology*, Satoshi Ebata and colleagues[3] report the results of the randomised, double-blind, placebo-controlled DESIRES clinical trial which investigated the efficacy and safety of rituximab in patients with systemic sclerosis. Patients were randomly assigned (1:1) to receive either rituximab (375 mg/m^2) or placebo intravenous infusions once per week for 4 weeks. The primary endpoint was the absolute change in modified Rodnan Skin Score (mRSS) at 24 weeks after initiation of study treatment. 54 patients received at least one dose of rituximab or placebo. The change in mRSS at 24 weeks was significantly lower in the rituximab group than in the placebo group (–6·30 in the rituximab group *vs* 2·14 in the placebo group; difference –8·44 [95% CI –11·00 to –5·88]; p<0·0001),[3] which represents a clinically meaningful improvement with rituximab.[4] The occurrence of adverse events and adverse drug reactions were similar between the two groups. Secondary endpoints included those related to interstitial lung disease and quality of life and function. The change in percentage of predicted forced vital capacity (FVC% predicted) at 24 weeks from