Rheumatology at the center of coronavirus disease 2019: pathogenesis, treatment, and clinical care

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The first case of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus 2019 (COVID-19), was reported in Wuhan, China in December 2019 [1]. Cases increased exponentially and quickly spread across the globe, reaching pandemic levels and becoming an international health crisis [2]. As of 22 May 2021, there have been 165 772 430 cases of COVID-19 reported to the WHO, including 3 437 454 deaths [3]. The entirety of the healthcare community, including rheumatologists, adapted seemingly overnight to this new medical reality – including reassignment of practitioners to the care of patients with COVID-19 from their normal duties and the heavy reliance on telemedicine to continue routine, maintenance care [4,5].

Rheumatology, perhaps unexpectedly, quickly emerged as a key medical discipline in the fight against COVID-19. In addition to direct redeployment to hospitals for the care of patients with COVID-19, the field took part in a massive undertaking to characterize infection and its impact on our patients. Rapidly, epidemiologic and cohort studies from across the globe emerged, showing that, in general, patients with immune-mediated inflammatory diseases (IMIDs) who developed COVID-19 did not have worse outcomes (i.e. hospitalization and death) compared with non-IMID patients [6–9]. Additionally, while most immunomodulatory therapy had no effect on outcomes, glucocorticoids appeared to increase the risk of hospitalization, while alternatively, tumor necrosis factor inhibitors were found to possibly decrease the risk of poor outcomes [9,10]. These findings allowed practitioners to confidently keep patients with IMID on their medications through the pandemic, likely preventing a heavy burden of disease flares. Importantly, as evidence emerged that many of the poor outcomes from COVID-19 may actually be because of a hyperinflammatory response [11,12] and that immunomodulatory medications may play a role in the treatment of acute infection [13–15], the expertise of rheumatologists became even more essential.

Our understanding of COVID-19 pathogenesis, therapeutics, and prevention has evolved significantly in just 1 year. And yet, even as at least a proportion of the world is finally emerging from the pandemic, important questions are yet to be addressed as they will undoubtedly impact the lives of patients with IMID and the research agenda for years to come.

The notion that viruses can serve as triggers for IMID is not novel. Viral illnesses have been well documented to be the initial drivers for a variety of autoimmune diseases, such as hepatitis C [16] leading to cryoglobulinemia, and HIV promoting psoriasis [17]. Recent studies have shown high rates of autoantibody production in patients hospitalized with COVID-19, including high rates of antinuclear antibody (ANA) positivity and antibodies associated with antiphospholipid syndrome [18,19]. Chang *et al.* found that almost 50% of patients with COVID-19 had at least one autoantibody, some of which may be pathogenic. Furthermore, the development of new antibodies was positively correlated with immune response to SARS-CoV-2 and, when a small cohort of patients with COVID-19 infection was followed longitudinally, one-third of them developed at least one new autoantibody at the second time point [20]. Another small study found that patients can show higher rates of autoantibodies even months after COVID-19 infection [21].

However, it is important to remember that the presence of autoantibodies does not translate directly into clinical autoimmunity. Autoantibodies, especially ANA and rheumatoid factor, are notoriously nonspecific and have been associated with multiple infectious processes (i.e. tuberculosis) without an associated development of IMID [22]. Although there have been case reports of new autoimmune diseases (most notably autoimmune hemolytic anemia and Guillain–Barre syndrome) after infection with SARS-CoV-2 [23], definite causality

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could not be attributed to COVID-19. A recent epidemiologic study from the United Kingdom, for example, found that the incidence of Guillain–Barre syndrome was actually lower in the period between March and May 2020 as compared with this same period in 2016–2019 [24].

Although SARS-CoV-2 has demonstrated a possible cross-reactivity with human tissue [25], there is not sufficient evidence to associate COVID-19 to the triggering of de novo autoimmunity. Long-term studies, many of which are currently underway, are needed to better answer this question.

The rapid development of vaccines for COVID-19 has presented new hope for global recovery from this pandemic. Data regarding the mRNA COVID-19 vaccine safety and efficacy are rapidly emerging for immunocompetent adult populations, where more than 90% of subjects develop adequate humoral response [26]. However, patients with IMID were not included in these original studies despite the fact that these individuals may have an inherently heightened susceptibility to infection. Moreover, the strength of response to viral vaccines (i.e. influenza and hepatitis B) and their long-lasting protective effects in IMID patients taking certain disease-modifying antirheumatic drugs (DMARDs), may not be as robust as it is in the general population following immunization [27–31]. Therefore, it is imperative to better understand the effect of these vaccinations in our patient population.

Although very early studies showed no difference in immunogenicity for patients with IMID [32], further evidence is emerging that specific immunomodulatory treatments, and possibly even IMIDs themselves [33], may reduce immunogenicity. In terms of immunomodulatory therapies, methotrexate [34,35], and rituximab [34,36,37] specifically have been identified as potentially decreasing humoral response to mRNA COVID-19 vaccinations. Mycophenolate mofetil [36,38], identified in the organ transplant literature, may also suppress the humoral response. Additionally, methotrexate was found to reduce the cellular response to the BNT162b2 mRNA vaccine as activated CD8+ T cell and the granzyme B-producing subset of these activated CD8+ T cells were not induced after vaccination in patients on methotrexate, despite being induced in both healthy controls and patients with IMID on other immunomodulatory medications in one cohort [8]. However, despite these findings, it is unclear what antibody level would correspond to vaccine clinical efficacy. Additionally, these patients were followed for generally short periods of time and longer term studies will be needed to assess whether these therapies may delay, rather than prevent antibody response. Critically, confirmation studies will be required to determine whether alternative strategies, such as additional vaccination doses or alteration of immunomodulator treatment dosing, is warranted. This is of particular importance as future immunization boosters against COVID-19 will likely be necessary.

As we move past the 1-year mark of the pandemic, studies found that even months after recovering from COVID-19, many patients continue to experience symptoms, such as fatigue, dyspnea, joint pain, muscle weakness, chest pain, and cough [39,40]. This new syndrome has now been dubbed *long haul COVID-19*. Although many of these patients are being evaluated by rheumatologists, the underlying pathophysiology of this syndrome remains unclear. Hypothesized mechanisms include: virus-specific changes, organ damage or inflammation because of acute infection, new autoimmunity because of immunologic aberration or tolerance breakdown because of acute infection, post critical illness sequalae, or, possibly, a completely unknown mechanism [41].

Currently, these patients require multidisciplinary care and urgent translational and epidemiologic studies are needed to explore the extent and underlying cause of this syndrome. If an immune-mediated inflammatory cause is identified, rheumatologists will again play a central role in the management of these patients. Furthermore, clinical trials using immunomodulators are also likely given their current role in acute infection, and with our knowledge and experience with the chronic use of these medications, rheumatologists will be needed to lead these endeavors.

As we look toward the future, we want to acknowledge patients across the globe who have participated in our studies during this particularly difficult year and the researchers who redirected their time and efforts to understanding and treating COVID-19. Our rapid accumulation of knowledge has allowed us to treat our patients more effectively. Indeed, over the course of the pandemic, rheumatologic patients have seen lower rates of hospitalization, higher level of care, mechanical ventilation, and even death [42]. As we our turn attention to the long-term effects of COVID-19 and vaccination strategies, this should also help us expand our knowledge of the interaction between infectious disease, immunology, and autoimmunity, and provide renewed insights into pathogenesis and therapeutic targets.

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Conflicts of interest

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