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Editorial

COVID-19 and Immunomodulatory Therapy — Can We Use Data from Previous Viral Pandemics?

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The implications of COVID-19 are wide-ranging for specialties such as rheumatology in which immunomodulatory therapies are prescribed. There has been much trepidation among many healthcare professionals regarding the best course of management during this time. This pandemic has also left many national policy makers perplexed because of our limited knowledge of the effects of COVID-19 in patients with rheumatic disease. Such limitations have resulted in variable evolving guidance among rheumatologists around the globe.

The British Society of Rheumatology (BSR) has recently published guidance to help stratify patients according to their level of risk and advise self-isolation or shielding measures for patients in high-risk groups[1]. Patients are advised to pause immunomodulation [except glucocorticoids (GC), hydroxychloroquine (HCQ), and sulfasalazine (SSZ)] if symptoms consistent with COVID-19 infection develop and to discuss re-initiation of therapy with their rheumatology team. The potential for the virus to persist subclinically in some individuals for an extended period of time after symptom resolution leaves a degree of apprehension among healthcare professionals regarding restarting therapy when an individual becomes asymptomatic. Other European societies, for example the Spanish Society of Rheumatology (SSR), similarly do not specify a time frame for restarting therapy, whereas the American College of Rheumatology (ACR) recommend re-initiation following a negative COVID-19 test or 2 weeks after symptom resolution[2,3]. The ACR, unlike the BSR, recommends temporary cessation of SSZ if infective symptoms develop, and also suggest cessation of nonsteroidal antiinflammatory drugs (NSAID), which differs from other international recommendations[3]. Although the SSR does not specify the continuation of HCQ, it notes that this, as well as other drugs [e.g., interleukin 6 (IL-6) or IL-1 and Janus kinase (JAK) inhibitors)] may be continued depending on local protocols[2]; similarly, the ACR suggests that IL-6 inhibitors may be continued in some cases as part of a shared decision-making process[3]. Although national bodies agree on the initiation of disease-modifying therapy in newly diagnosed patients with very active disease, starting with conventional, lower-risk agents, the BSR outlines specific recommendations, for example initiation of HCQ or SSZ, where appropriate, rather than methotrexate (MTX) or leflunomide (LEF), or agents with shorter half-lives [such as etanercept (ETN)] in patients who meet the criteria for biologic initiation, if benefits outweighs the risks[1]. The lack of international consensus on certain aspects of management, however, adds to the apprehension among healthcare professionals.

Reviewing data published during similar viral outbreaks in the past, such as the Severe Acute Respiratory Syndrome (SARS), Middle Eastern Respiratory Syndrome (MERS), or H1N1 (influenza A) pandemics (2002–2004, 2012, and 2009–2010, respectively), however, may shed light on aspects of management that require further consideration. In particular, SARS and COVID-19 are remarkably alike — the genomes of the coronaviruses causing these diseases have 82% nucleotide identity[4]. Further, the angiotensin-converting enzyme 2 in the lower respiratory tract has been demonstrated to be a cell entry receptor for both viruses[5]. COVID-19, however, has affected the world on an amplified scale owing to increased transmissibility, highlighting our need for increased understanding of viral differences at genomic/proteinomic levels. To date, the major distinctions between the two are in *ORF3b, Spike*, and *ORF8* genes, although the exact functions of the encoded proteins have yet to be determined[4].

Despite concerns, it remains unclear whether patients receiving immunomodulation are more likely to contract COVID-19 than members of the general population, and if contracted, whether such treatments result in a higher rate of complications, for example, secondary bacterial pneumonia or acute respiratory distress syndrome. Limited data to date,

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however, suggest that contraction risk plus worse disease is not the case; this may be because the host innate immune system appears to be the main driver of lung inflammation[6]. Monti, *et al* report a retrospective survey-based study of 13 rheumatology patients receiving biologic or synthetic targeted therapy from Lombardy, Italy, who either tested positive, had highly suggestive features, or had known contact with someone with COVID-19. The study revealed no cases of severe respiratory complications or deaths, and only 1 patient (aged 65 yrs) required hospital admission for low-flow supplemental oxygen[7]. These patients had a diagnosis of either rheumatoid arthritis (RA) or spondyloarthritis (SpA) and patients who were confirmed to have or had clinical features highly suspicious of COVID-19 were taking a variety of immunomodulatory therapies [ETN, abatacept (ABA), or tofacitinib, with concomitant use of MTX, LEF, HCQ, or low-dose GC (≤ 5 mg/day prednisolone equivalent)][7]. Further, among 700 patients admitted to that hospital for severe COVID-19, none were receiving biologic or synthetic targeted therapy, suggesting that patients receiving immunomodulatory therapy may not be at increased risk of respiratory or life-threatening complications compared to the general population[7].

In a recently published audit of critical care centers in the United Kingdom, of the 775 patients admitted with COVID-19–related symptoms, only 3% (22 patients) were deemed to be immunocompromised prior to admission compared to 8.8% of patients admitted for a viral pneumonia prior to this pandemic (2017–2019)[8]. These statistics may reflect the extra caution taken by patients receiving immunosuppressive therapies during this time rather than that COVID-19 is less likely to cause severe respiratory symptoms in these patients compared to those with other viral pneumonias. There are no internationally reported data on fatalities from SARS, MERS, or COVID-19 to date in patients taking immunosuppressive agents (including those taking high doses to prevent posttransplant rejection)[6]. However, a recent publication describing 21 critically ill patients in Washington reports that 1 patient had a preexisting underlying rheumatological disease and 3 were receiving immunosuppressive therapy (including for a previous transplant) prior to COVID-19 infection, although specific details of immunosuppression were not reported[9]. Published data from China do not report rheumatological diseases or use of immunosuppressive or immunomodulatory therapy as a major risk factor for severe COVID-19 illness[10]; however, a retrospective study is ongoing.

Nonetheless there is concern regarding patients taking high-dose GC in particular, because that may boost viral replication of COVID-19 when taken during the early stages of viral infection[11]. Although this may not increase the clinical severity of disease, *per se*, it may result in increased transmissibility through enhanced viral shedding. There is again, however, a lack of objective data reporting these patients to be at increased risk of COVID-19 complications, and the definition of a high dose of GC in this situation remains ambiguous. Thus, various guidelines advocate use of the lowest effective dose of GC, if required[1,3].

The differences between national guidelines regarding the continuation of various disease-modifying drugs (such as HCQ or SSZ) raise further questions. Although there is biological plausibility regarding the beneficial effects of HCQ as well as the antibacterial effects of SSZ in patients with COVID-19, further research is required in this field; to date, various studies reviewing HCQ in this cohort demonstrate conflicting results[12].

An Italian study of 159 rheumatology patients taking biologic therapies [anti–tumor necrosis factor (TNF), rituximab (RTX), or ABA] during the H1N1 pandemic demonstrated higher viral infection rates compared to controls; interestingly, complication or hospitalization rates did not differ between groups[13]. Although there are notable differences between H1N1 and COVID-19, it is possible that our pickup rates of infected patients is skewed because many patients may only have mild symptoms. Therefore, the true incidence of COVID-19 among patients with immunosuppression remains largely unknown owing to a lack of reporting, either by patients to their clinical team or by healthcare professionals to international databases. A recent publication by Haberman, *et al* reported 86 patients with immune-mediated inflammatory disease (including those with RA, ankylosing spondylitis, and psoriatic arthritis as well as inflammatory bowel disease, psoriasis, and other non-rheumatological conditions) who had either confirmed or highly suspected COVID-19 infections[14]. The incidence of hospitalization within this cohort was 16%; this group was older compared to the cohort that was not hospitalized and also had higher incidence of comorbidities, such as chronic obstructive pulmonary disease and diabetes[14]. Interestingly, a lower percentage of the hospitalized group were receiving biologic or JAK inhibitors compared to the non-hospitalized group, whereas the use of oral GC, HCQ, and MTX was higher. Given the low numbers in this report, it is difficult to interpret these findings with any certainty; the development and increased uptake of databases, such as the COVID-19 Global Rheumatology Alliance, however, should enhance our knowledge of cases in the upcoming months[15]. To date, this registry has enabled the publication of data on 110 patients with rheumatological disease who were diagnosed with COVID-19, reporting their rheumatological diagnosis, medications, COVID-19 symptoms, and comorbidities. Although 35% of these patients were admitted to hospital (and 5% died), it is not possible to extrapolate from this early data whether the severity of disease was related to their rheumatological diagnosis/medications or other comorbidities[16].

Postinfective antibody levels seem to differ depending on the type of coronavirus; studies have shown a precipitous fall in antibody levels in patients who recovered from MERS; however, antibodies to SARS appear to persist even after 15 years postinfection. It remains unclear whether such antibodies are sufficient to prevent reinfection[16]. There are many unknowns regarding vaccine development against COVID-19, because antibody responses alone may not be sufficient. Further, the safety of such vaccines needs to be considered; an experimental SARS vaccine tested in ferrets

resulted in hepatitis, and there is also a risk of disease enhancement in vaccinated patients[17].

The immunogenicity of such vaccines in our immunosuppressed cohort also needs to be considered. Such data are unavailable regarding coronaviruses, but studies reviewing the immune response of patients taking biologic therapies used in rheumatology differ depending on the drug used. Although there are some studies that suggest that non-live vaccinations given during treatment with anti-TNF therapies may elicit immune responses lower than those that result when given to people not receiving treatment, data published by the European Medicines Agency (EMA) in the Summary of Product Characteristics report similar humoral responses to the influenza vaccine in patients with RA who are taking adalimumab and certolizumab compared to placebo[18]. Newer immunomodulators, such as tofacitinib and ABA in patients with RA, also demonstrated satisfactory responses compared to placebo, although the latter patient group did demonstrate a slight reduction of immunogenicity. Interestingly, the data reported patients taking both certolizumab and MTX, and tofacitinib and MTX combination therapy resulted in an immune response lower than that found in those taking biologic/small molecule monotherapy[18]. The EMA also reported a study of the influenza vaccine in healthy volunteers treated with secukinumab compared to placebo; the biologic cohort did not demonstrate a suppressed humoral immune response to the vaccine[18]. Studies of H1N1 immunogenicity in rheumatology cohorts have, however, demonstrated a significantly reduced antibody response in patients with RA taking RTX compared to those with RA or SpA and taking other therapies (anti-TNF, ABA, tocilizumab, anti-TNF, and MTX combination therapy or NSAID). Patients taking other forms of immunosuppression (including dual therapy, such as anti-TNF therapy and MTX) showed low though acceptable antibody responses[19]. Although these data relate to the immunogenicity to influenza vaccines alone, it is pertinent for us to consider this information when hypothesizing the effectiveness of a potential COVID-19 vaccination in our cohort of patients.

There is evidence to suggest that adjuvant vaccines are likely to elicit higher immune responses in patients taking biologic agents[17], though depending on the type of vaccination there may be a benefit of temporarily pausing immunosuppressive therapy (especially MTX), where possible, for a period pre- and/or post-vaccination to improve viral immunity. Further, studies of influenza vaccines in patients with RA have demonstrated increased immunogenicity to the high-dose trivalent vaccine compared with the standard-dose quadrivalent vaccine[20]. Thus, appropriate dosing of a potential vaccine against COVID-19 will need to be assessed in our patient cohort.

For now, we do not have robust evidence on how immunomodulators affect patients with rheumatic disease in relation to COVID-19. It is therefore important that these patients are assessed on composite clinical risk scores and that careful review is made of the risk/benefit for maintenance and initiation of disease-modifying antirheumatic drugs. It is imperative that real-world evidence of patients with rheumatic diseases and their outcomes is recorded in relation to COVID-19 to build up a body of evidence, which may help inform present and future pandemics. For now, we may consider the words of Sir William Osler: "The good physician treats the disease. The great physician treats the patient with the disease."

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