COVID-19 and Rheumatology patients on immunomodulatory therapy - can we extrapolate data from previous viral pandemics?

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The implications of COVID-19 are wide-ranging for specialties, like Rheumatology, where immunomodulatory therapies are prescribed, and there has been much trepidation amongst many healthcare professionals regarding the best course of management during this time. This pandemic has also left many national policy-makers perplexed due to our limited knowledge of the effects of COVID-19 in patients with rheumatic disease. Such limitations have resulted in variable evolving guidance amongst 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, hydroxychloroquine and sulfasalazine) 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 amongst 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 timeframe for restarting therapy, whereas the American College of Rheumatology (ACR) recommend re-initiation following a negative COVID-19 test or two weeks after symptom resolution [2,3]. ACR, unlike the BSR, recommend temporary cessation of sulfasalazine if infective symptoms develop, and also suggest cessation of non-steroidal anti-inflammatory drugs (NSAIDs), which differs from other international recommendations [3]. Although the SSR do not specify the continuation of hydroxychloroquine, they note that this, as well as other drugs (e.g. interleukin (IL)-6 or IL-1 and Janus Kinase (JAK) inhibitors), may be continued depending on local protocols [2]; similarly, the ACR suggest 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 hydroxychloroquine or sulfasalazine, where appropriate, rather than methotrexate or leflunomide, or agents with shorter half-lives (such as etanercept) 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 amongst 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]; furthermore, the angiotensin-converting enzyme 2 (ACE2) 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 due 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 on 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 (ARDS). Limited data to date, however, suggests that this is not the case; this may be as the host innate immune system appears to be the main driver of lung inflammation [6]. Monti et al. (2020) report a retrospective survey-based study of 13 Rheumatology patients on biologic or synthetic targeted therapy from Lombardy, Italy, who either tested positive, had highly suggestive features or had a known contact with someone with COVID-19 revealed no cases of severe respiratory complications or deaths, and only one patient (aged 65 years) required hospital admission for low-flow supplemental oxygen. These patients had a diagnosis of either rheumatoid or spondyloarthritis and patients who were confirmed to have or had clinical features highly suspicious of COVID-19 were on variety of immunomodulatory therapies (etanercept, abatacept or tofacitinib, with concomitant use of methotrexate, leflunomide, hydroxychloroquine or low-dose glucocorticoids (≤5 mg/day prednisolone equivalent)) [7]. Furthermore, among 700 patients admitted to that hospital for severe COVID-19 none were on biologic or synthetic targeted therapy, suggesting that patients on 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 centres in the UK, 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 due to a viral pneumonia prior to this pandemic (2017-2019) [8]. These statistics may reflect the extra caution taken by patients on immunosuppressive therapies during this time rather than a true reflection that COVID-19 is less likely to cause severe respiratory symptoms in these patients compared to those with other viral pneumonias. There is no internationally reported data on fatalities in patients on immunosuppressive agents (including those on high doses to prevent post-transplant rejection) from SARS, MERS or COVID-19 to date [6], however a recent publication describing 21 critically-ill patients in Washington reports that one patient had a pre-existing underlying rheumatological disease and three were on 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.

There is an ongoing concern, however, regarding patients on high-dose glucocorticoids in particular, as this 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 via 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 glucocorticoids in this scenario remains ambiguous; as such, various guidelines advocate use of the lowest effective dose of glucocorticoids, if required [1, 3].

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

An Italian study of 159 Rheumatology patients on biologic therapies (anti-tumour necrosis factor (TNF), rituximab or abatacept) during the H1N1 pandemic demonstrated higher viral infection rates compared to controls; interestingly, complication or hospitalisation rates did not differ between groups [13]. Although there are notable differences between H1N1 and COVID-19, it is possible that our pick-up rates of infected patients is skewed as many patients may only have mild symptoms and therefore the true incidence of COVID-19 amongst patients on immunosuppression remains largely unknown due 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. (2020) reported 86 patients with immune-mediated inflammatory disease (including those with rheumatoid arthritis, 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 hospitalisation within this cohort was 16%; this group was older compared to the cohort who were not hospitalised and also had higher incidence of co-morbidities, such as chronic obstructive pulmonary disease and diabetes [14]. Interestingly, a lower percentage of the hospitalised group were receiving biologic or JAK inhibitors compared to the non-hospitalised group, whereas the use of oral glucocorticoids, hydroxychloroquine and methotrexate was higher [16]. 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 reviewing data of 110 patients with rheumatological disease diagnosed with COVID-19, reporting their rheumatological diagnosis, medications, COVID-19 symptoms and co-morbidities; although 35% of these patients were admitted to hospital (and 5% died), again, it is not possible to extrapolate whether the severity of disease was related to their rheumatological diagnosis/medications or other co-morbidities from this early data [16].

Post-infective 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 post-infection; it remains unclear, however, whether such antibodies are sufficient to prevent re-infection [16]. As such, there are many unknowns with regards to vaccine
development against COVID-19, as antibody responses alone may not be sufficient. Furthermore, 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 is unavailable with regards to Coronaviruses, however studies reviewing the immune response of patients on 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 lower immune responses to those not on treatment, data published by the European Medicines Agency (EMA) in the Summary of Product Characteristics (SmPC) report similar humoral responses to the influenza vaccine in patients with rheumatoid arthritis (RA) on adalimumab and certolizumab compared to placebo [18]. Newer immunomodulators, such as tofacitinib and abatacept in RA patients also demonstrated satisfactory responses compared to placebo, although the latter patient group did demonstrate a slight reduction of immunogenicity. Interestingly the data reported patients on both certolizumab and methotrexate, and tofacitinib and methotrexate combination therapy mounted a lower immune response to those on 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 on rituximab compared to those with RA or spondyloarthritis on other therapies (anti-TNF, abatacept, tocilizumab, anti-TNF and methotrexate combination therapy or NSAIDs); patients on other forms of immunosuppression (including those of dual therapy, such as anti-TNF therapy and methotrexate) showed low though acceptable antibody responses [19]. Although this data relates to the immunogenicity to influenza vaccines alone, it is pertinent for us to consider this information when hypothesising the effectiveness of a potential COVID-19 vaccination in our cohort of patients.

There is evidence to suggest that adjuvanted vaccines are likely to elicit higher immune responses in patients on biologic agents [17], though depending on the type of vaccination there may be a benefit of temporarily pausing immunosuppressive therapy (especially methotrexate), where possible, for a time-period pre- and/or post-vaccination to improve viral immunity. Furthermore, studies on influenza vaccines in patients with RA have demonstrated increased immunogenicity to the high-dose trivalent vaccine compared with the standard-dose quadrivalent vaccine [20]; as such, 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 careful review made of the risk/benefit for maintenance and initiation of disease modifying anti-rheumatic 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 this 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.”
References


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