Short Communication

Coronavirus Disease-2019: Implication for the care and management of patients with systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus is a chronic remitting-relapsing autoimmune disease that affects multiple organ systems. In this article we discuss aspects in the management of lupus patients that are particularly relevant during the current SARS-CoV-2 pandemic. We speculate that lupus patients might be more susceptible for a more severe COVID-19 disease course and emphasize the importance of maintaining remission in lupus patients. We discuss the critical role hydroxychloroquine plays in the management of lupus patients and suggest considering the psychosocial implications of the current pandemic on lupus care.

Keywords: COVID-19, cytokine storm, hydroxychloroquine, immunosuppression, lupus, SARS-CoV-2

A recently emerged single-stranded RNA virus of the *Coronaviridae* family (severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2) has resulted in a pandemic associated with sometimes severe and life-threatening respiratory infection (1, 2). The disease caused by SARS-CoV-2, known as Coronavirus Disease-2019 (COVID-19), is more likely to cause a severe infection in older individuals and patients with underlying medical conditions, although younger individuals have had serious and even life-threatening disease (2). Analysis of available data suggests that patients with chronic medical illnesses such as diabetes, cardiovascular disease, and chronic pulmonary disease are particularly at increased risk for a complicated disease course (3). Data on patients with rheumatologic autoimmune diseases are currently lacking. Efforts in the form of registries to report and analyze the outcome of COVID-19 in patients with rheumatological diseases, including the COVID-19 Global Rheumatology Alliance and the EULAR-COVID-19 Database will be particularly fruitful as data become available in the near future (https://covidibd.org/ and https://www.eular.org/eular_covid19_database.cfm; both accessed on April 3, 2020).

Systemic lupus erythematosus is a chronic autoimmune disease characterized by a remitting-relapsing course. At the present time, we do not know how lupus will affect the susceptibility and disease course of COVID-19 in patients infected with SARS-CoV-2. Nonetheless, there are characteristics of the disease that might have relevant consequences, and specific implications that are important to consider in taking care of lupus patients during the current COVID-19 pandemic.

Immunosuppressive medications

Many lupus patients are treated with immunosuppressive medications to keep their disease under control and prevent organ complications. Medications such as azathioprine, mycophenolate mofetil, methotrexate, belimumab, and rituximab, among others are commonly used. Some patients might also be taking glucocorticoids especially during disease flares, although the goal is always to use the lowest dose and for the shortest duration possible when glucocorticoids are part of the treatment of lupus patients.

The general thinking is that people with an immunosuppressed state, including those on immunosuppressive medications are more prone to infections. Indeed, infections remain a leading cause of mortality in lupus patients (4). However, we do not have specific data to suggest that medication-induced immunosuppressed state in lupus predisposes patients to SARS-CoV-2 infections. Limited data available from transplant patients who are also treated with immunosuppressive medications suggest that they do not have a higher frequency of more severe COVID-19 (5). We do not know if this will be true in lupus patients, as the underlying immune dysregulation of lupus might be an important factor. We believe that

maintaining disease remission in lupus patients, especially during a pandemic infection, is extremely important (see below), not only to avoid unnecessary office and emergency room visits, but hospitalizations, all of which increase potential exposure to COVID-19. As such, until there is evidence to the contrary, these authors suggest that lupus patients continue to take their immunosuppressive medications as they did before the pandemic. This includes avoiding discontinuation or lowering doses of any immunosuppressive medication, unless clinically indicated. However, some modifications may be considered on a case by case basis as appropriate. For example, belimumab can be effectively administered by intravenous infusion or subcutaneous injections. One might consider using the subcutaneous route if possible to avoid the risk associated with going to an infusion center.

Maintaining disease remission

Given the pathophysiology of lupus we argue that maintaining disease remission is of utmost importance during this pandemic. Lupus is characterized by a DNA methylation defect in multiple cell types, which is particularly well studied in T cells and leads to over-expression of methylation sensitive genes (6). The DNA methylation defect in lupus patients is sensitive to the levels of oxidative stress. Most environmental factors that trigger lupus flares are associated with increased oxidative stress which has been shown to exaggerate the DNA methylation defect in lupus patients (7). In a recent report we show data to suggest that the *ACE2* gene, which encodes the attachment receptor for SARS-CoV-2, is de-methylated and overexpressed in lupus patients (8). Therefore, we speculate that if lupus is allowed to flare, then *ACE2* demethylation and overexpression may be exaggerated which could lead to enhanced susceptibility to SARS-CoV-2 infection. This may represent one potential mechanism to support maintenance of effective medications in lupus and avoidance of disease flares.

Hydroxychloroquine shortage

Hydroxychloroquine is the cornerstone treatment for lupus patients. This anti-malarial is one of only four medications currently approved for lupus by the U.S. Food and Drug Administration. Hydroxychloroquine is associated with reduction in lupus flares (9), reduction in organ damage complications from lupus (10, 11), reduction in treatment failure in lupus nephritis (12), improved overall survival of lupus patients (13), and lower risk of preeclampsia during pregnancy in lupus (14). Lupus is an independent risk factor for cardiovascular dis-

ease with higher rates of myocardial infarction than expected (15). In this regard, hydroxychloroquine has been shown to reduce lipid levels, including LDL cholesterol and triglyceride levels (16, 17), reduce the risk of thrombosis due to anti-platelet effects (18, 19), and improve blood sugar control (20).

The potential shortage of hydroxychloroquine for patients with lupus due to the redirection of supply toward treatment of COVID-19 is concerning. There are no good substitutes for anti-malarials in terms of the favorable risk-benefit ratio for treatment of certain manifestations of lupus. Hydroxychloroquine was reported to have an anti-viral effect on SARS-CoV-2 *in vitro* (21, 22). A small non-randomized open-label study that examined the effect of hydroxychloroquine in combination with azithromycin in viral eradication of nasopharyngeal swabs in COVID-19 patients was recently published (23). The positive interpretation of these data has been challenged in a follow-up report (24). The open label studies and case series all require clinical trial confirmation, a number of which are already underway (ClinicalTrials.gov search on April 3, 2020 for COVID-19 and hydroxychloroquine shows 44 registered trials). Regardless of the limited data on effectiveness of hydroxychloroquine for treating COVID-19 infections, many institutions have developed expanded access protocols for critically ill patients. In addition, several companies have agreed to ramp up production of hydroxychloroquine to ensure no interruption of treatment for those with autoimmune conditions.

Interstitial lung disease and lupus pneumonitis

Patients with chronic pulmonary diseases are more prone to severe COVID-19 (3). Although relatively uncommon, up to 15% of lupus patients develop interstitial lung disease (ILD) (25). In this subset of patients, it is important to test for and recognize SARS-CoV-2 infection early, as respiratory symptoms such as dry cough and shortness of breath can be wrongly attributed to worsening of underlying connective tissue disease related ILD. The absence of fever should not lower the suspicion for a SARS-CoV-2 infection in patients with concerning exposures or other typical symptoms, particularly in those on immunosuppressive medications.

Approximately 1-4% of lupus patients develop acute lupus pneumonitis, which is characterized by fever, cough, shortness of breath, hypoxia, and pleuritic chest pain (25). We suggest that even in patients who are known to have lupus pulmonary involvement, presentation

with these symptoms should trigger testing for SARS-CoV-2 infection before a diagnosis of acute lupus pneumonitis can be made.

Routine clinic visits and laboratory studies

Lupus patients typically require regular follow up visits to ensure early detection of flares and to monitor the effectiveness and toxicity of immunosuppressive therapy. This may involve laboratory testing including routine and serologic analyses. Many institutions, including our own, have transitioned most patients to telephonic and video visits to minimize contact exposures and to practice effective social distancing. Avoiding face-to-face interactions should not preclude necessary laboratory monitoring or the occasional in person visit if necessary. In these situations, use of appropriate personal protective equipment (masks, etc) and timing visits when volumes are lowest are prudent. If laboratory testing can be safely delayed, then consideration for this may be made based on good clinical judgement.

Cytokine storm

A subset of patients with COVID-19 develop severe immune activation in response to SARS-CoV-2 infection resulting in a sepsis-like picture, acute respiratory distress syndrome (ARDS), and multi-organ failure. This is characterized by a fulminant increase in cytokine levels including IL-2, IL-6, IL-7, IL-10, interferon-γ, macrophage inflammatory protein 1-α, and tumor necrosis factor-α, among others (1, 26). This "cytokine storm" is reminiscent of secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome (secondary HLH/MAS) (27). Indeed, secondary HLH is often triggered by viral infections (28). Autoimmune diseases, especially lupus, have been associated with increased risk for developing secondary HLH (28, 29). We have previously shown that interferon-regulated genes are robustly demethylated in lupus patients, suggesting that these genes are primed for a rapid response in the presence of type-I interferons, which is a typical immune response to viral infections (30, 31). We have also shown that key cytokine regulating genes, such as NFκB, are also progressively hypomethylated in lupus CD4+ T cells as the disease becomes more active (32). It can be speculated that lupus patients might be at increased risk for cytokine storm during SARS-CoV-2 infection. Indeed, lupus patients are inherently more susceptible to viral infections and an underlying mechanism for this observation has been recently elucidated (33). A non-peer reviewed report from China suggested that intravenous tocilizumab resulted in rapid fever and supplemental oxygen reduction within days of administration (34). There

are a number of ongoing trials to determine if blocking cytokine responses using anakinra (IL-1 receptor antagonist) or tocilizumab (IL-6 receptor antagonist) improves outcome in COVID-19 patients (ClinicalTrials.gov search on April 5, 2020 for COVID-19 and anakinra and COVID-19 and tocilizumab showed 3 and 12 registered trials, respectively). Measuring markers of cytokine hyper-responsiveness, such as serum ferritin levels and C-reactive protein, early in the course of COVID-19 infection may predict those most likely to develop cytokine storm. We believe that if treatment directed at the cytokine response were to be considered, it would more likely to be effective and more impactful if given at the earliest sign of cytokine hyper-responsiveness (personal communication, Dr. Scott Canna, Division of Pediatric Rheumatology, University of Pittsburgh). However, caution must always be practiced when deciding on initiating immunosuppressive therapy in the setting of infection without sufficient data to support effectiveness. A small case series of 3 patients reported a possible benefit from intravenous immunoglobulin (35), and there remains conflicting data on the benefit of intravenous corticosteroids, although one large study out of China suggested that death rates were reduced in the setting of COVID-19 pneumonia with acute respiratory distress (36).

Psychosocial elements
Finally, it is important to recognize and address the psychosocial implications of the current pandemic on our lupus patients. This is a challenging time, with the constant barrage of news and reports of the devastation and loss of life from COVID-19 that is increasing worldwide and on a daily basis. It can be unsettling to hear of a potential shortage of a medication that many of our patients have come to rely on (hydroxychloroquine), or conflicting reports about both the increased risk of COVID-19 in immunosuppressed patients as well as a recent statement that lupus patients may be protected from getting COVID-19 while taking hydroxychloroquine. Neither report substantiated by data. Social distancing and drastic lifestyle changes to prevent viral spreading further add to the psychological distress. Needless to say, the economic consequences and loss of employment affecting our patients and their families can take a toll on their well-being. It is important that physicians remain vigilant to these psychological, social, and economic implications of the current COVID-19 pandemic. Stress is a well-recognized trigger that can precipitate lupus flares, and increase the need for medical intervention.

In summary, sufficient data are lacking regarding the susceptibility and severity of COVID-19 infection in lupus patients. We support aggressive measures to prevent exposure to SARS-CoV-2 infection, maintaining disease remission, and addressing psychosocial aspects to ensure the best possible outcomes for our patients during this pandemic. Supporting clinical trials, scientific investigation and patient registries will enhance our understanding of COVID-19 and the impact on autoimmune diseases. We must be a calm and steady voice of reason and the source of truth for our patients with lupus during this unprecedented time in world history.

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