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CHEST

When the Game Changes

Guidance to Adjust Sarcoidosis Management During the Coronavirus Disease 2019 Pandemic

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Over the past few months, the novel coronavirus disease 2019 (COVID-19) pandemic has posed many challenges for practicing physicians. Patients with sarcoidosis may have an increased risk of a poor outcome and death from COVID-19 infection for several reasons. First, sarcoidosis involves the lung in approximately 90% of patients,[1] many of whom have diminished baseline lung function with reduced pulmonary reserve should they develop respiratory failure. Second, although the etiology of sarcoidosis is unknown, it is postulated that immunologic dysfunction and dysregulation play essential roles in the development of the disease.[2] Third, African-American race and many comorbidities

ABBREVIATIONS: ADA = adalimumab; COVID-19 = coronavirus disease 2019; DMASD = disease-modifying antisarcoid drug; GC = glucocorticoid

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associated with glucocorticoid (GC) therapies such as hypertension, diabetes, and obesity have been identified by the Centers for Disease Control and Prevention as independent risk factors for COVID-19-related death and are more prevalent in sarcoidosis cohorts.[3] Finally, and most pertinent to the treating clinician, immunosuppressive medications are the primary agents used for the treatment of sarcoidosis, particularly GCs, which are often the first-line agent.[4]

Little is known about the impact of sarcoidosis treatments on susceptibility to and disease expression of COVID-19 infection; however, because of the lethality of COVID-19 infection, there is concern that the risk-benefit ratio of effective immunosuppressive therapies for sarcoidosis may be altered in the current climate. The goal of the present article was to provide clinicians with practical guidance on how to adjust immunosuppressive therapy for the treatment of sarcoidosis during the COVID-19 pandemic. This guidance does not reflect a change in the standard of care of sarcoidosis but rather stresses the importance of minimizing the dose of immunosuppression, which is the accepted practice in the management of sarcoidosis. Given the current COVID-19 pandemic and the increased risk of a poor outcome in individuals receiving immunosuppression who become infected, these guidelines emphasize adherence to this principle. This document should be considered an opinion statement to provide guidance to the clinician based on expert opinion. Whenever possible, the authors have attempted to extrapolate the outcomes of infections in patients with sarcoidosis from what is known in other populations who receive similar medications.

Many of the immunosuppressive agents used to treat sarcoidosis are used in rheumatic diseases. Based on systematic reviews and meta-analyses, it is known that these drugs, notably systemic GCs and biologic agents (eg, tumor necrosis factor inhibitors), increase the risk for serious infections.[5,6] Traditional steroid-sparing agents, most importantly methotrexate, are also associated with an increased risk of infection, but the degree of risk depends on the nature of the underlying illness, dosage, treatment duration, and infection in question.[7] This degree of risk is generally considered to be lower than that with GCs and biologic agents.[7,8]

Although lowering immunosuppression might improve the outcome of a patient with sarcoidosis who becomes exposed to COVID-19, it is also associated with the risk of worsening sarcoidosis. In practice, treating physicians are confronted with two general scenarios: first, a patient who is clinically quiescent maintained on a stable medical regimen; or second, a patient with active, organ-threatening disease.

Management of a Clinically Stable Patient With Few or No Symptoms and No Severe Organ Manifestations

If a patient with stable sarcoidosis is receiving GC therapy alone, an attempt can be made in most cases to slowly reduce the corticosteroid dose. Notably, in a randomized trial with GC tapering, a high proportion of patients receiving placebo were successfully able to taper their prednisone dosage by $>$ 50% without flares of the disease over several months.[8] In one study of 36 patients with pulmonary sarcoidosis who had a pulmonary exacerbation, none was receiving more than 10 mg/d of prednisone at the time of their exacerbation.[9] Even exacerbations of pulmonary disease usually do not result in significant respiratory distress and typically respond to modest increases in corticosteroid dosages for just a few weeks. Skin sarcoidosis is a specific, non-life-threatening form of the disease in which it may be prudent to attempt to taper therapy.

In patients with stable disease who are currently on disease-modifying antisarcoid drugs (DMASDs) such as methotrexate, mycophenolate mofetil, azathioprine, and others, de-escalation of therapy should be considered. This can be achieved by reducing the dose or prolonging the dosing interval. For example, if a patient is stable on weekly methotrexate, a dose reduction or dosing every other week instead of every week are reasonable options. An outright drug holiday for several weeks, while risk-benefit is continually reassessed, may be considered for some patients, but this approach could increase the chance for more abrupt sarcoidosis flares that may be more refractory to control and prompt additional GC therapy. It is re-emphasized that DMASDs may present lower risk of infections than GCs. In patients who are receiving antimalarial agents such as chloroquine or hydroxychloroquine, we suggest continuing therapy. Unfortunately, because of preliminary, inconclusive reports suggesting a potential benefit of hydroxychloroquine in the treatment of COVID-19,[10] widespread shortages have ensued.

Patients who receive immunosuppressive biologic agents may be at increased risk of COVID-19 infection. However, because of concern for rebound sarcoidosis

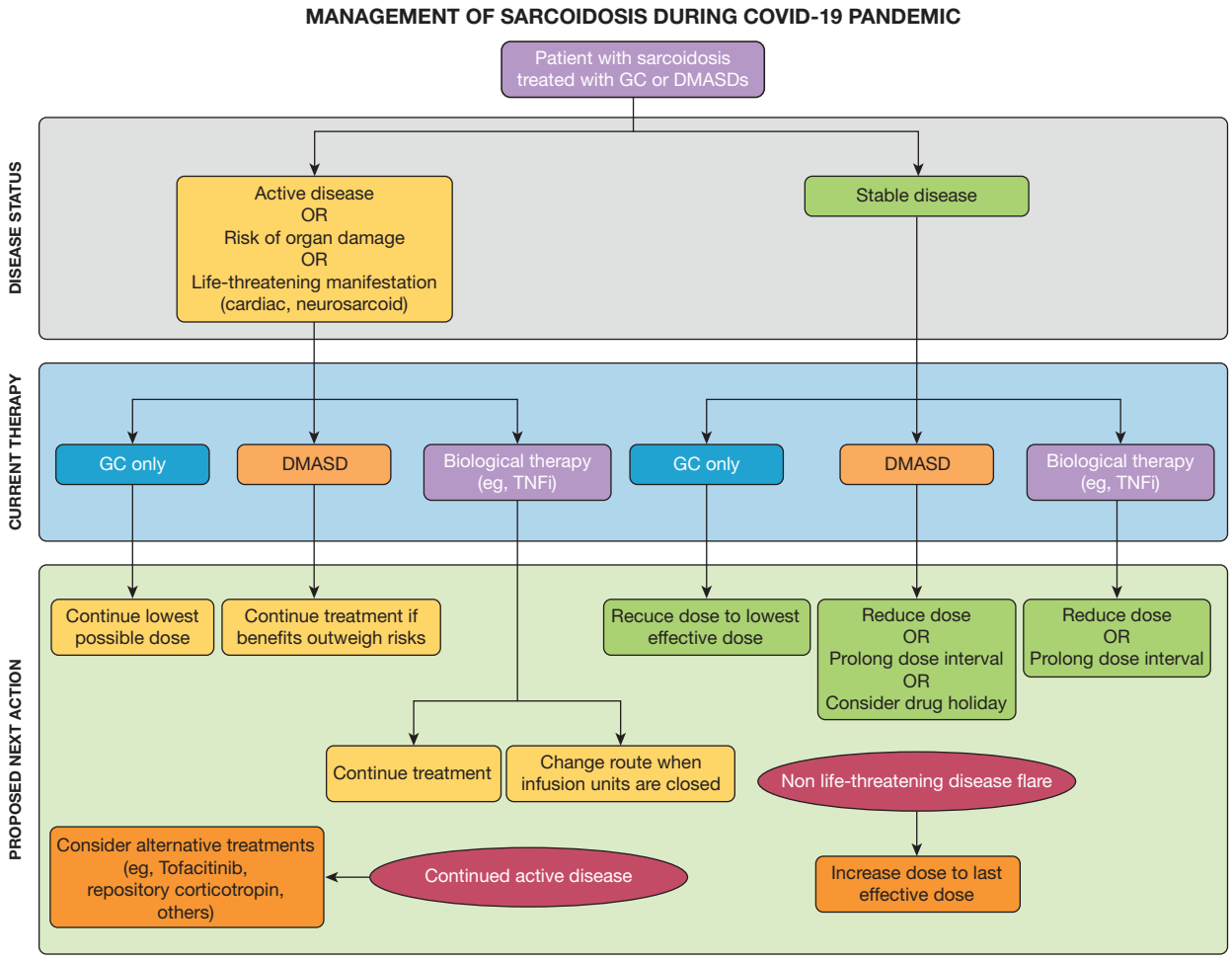

Figure 1 – *Proposed management algorithm of immunosuppression for sarcoidosis during the COVID-19 pandemic. Our recommended approach for two types of patients is depicted: the clinically stable patient who is in remission with therapy, and the patient with continued, active disease or organ dysfunction requiring continued immunosuppression. Details are given in the text. COVID-19 = Coronavirus Disease 2019; DMASD = disease-modifying antisarcoid drug; GC = glucocorticoid; TNFi = tumor necrosis factor inhibitor.*

flares, which may be problematic to control if these medications are discontinued abruptly, a gradual dose reduction could be considered. For example, infliximab may be given less frequently (eg, every 6 to 8 weeks instead of monthly) or at a lower weight-based dose (eg, 3 mg/kg instead of 5 mg/kg of body weight). In addition, premedication with GC could be reduced significantly or eliminated from the infusion protocol. When DMASDs are used for prevention of antibody formation in patients taking tumor necrosis factor inhibitors, a low dose (eg, methotrexate 10 mg weekly) is considered effective.[11]

If immunosuppression is reduced, clinicians should instruct patients with sarcoidosis to be vigilant for any changes in their condition that are suggestive of active disease. The clinician should establish facile methods of communication with their patients, including rapid consultation systems (eg, telemedicine) and other appropriate safeguards.

Management of Patients With Clinically Active, Organ- or Life-Threatening Disease

In patients with sarcoidosis and organ or life-threatening disease, a significant dose reduction or discontinuation of therapy may be contraindicated because of the risk of severe unfavorable outcomes. Such patients include those with progressive pulmonary disease, cardiac disease, uveitis, or neurosarcoidosis.

Patients who are on GC therapy alone should be managed with the lowest possible dose to achieve disease control. If very high doses of GC (eg, > 40-60 mg/d of prednisone) are necessary, the addition of a DMASD may be prudent to enable a reduction in GC requirements, because GC therapy is associated with a

high risk of infection in patients with sarcoidosis.[12] Such patients who have been stabilized on DMASDs should probably be maintained on current dosages. In patients on biologic therapies such as infliximab and adalimumab, therapy also should probably be continued because of the consequences of disease relapse. Due to logistic concerns (eg, potential closure of infusion units), switching to home infusion of infliximab or to subcutaneous adalimumab may be considered in carefully selected patients. In patients with active disease who cannot receive biologic therapies for logistic or clinical reasons, alternative treatments such as tofacitinib, repository corticotropin, or others may be considered on a case-by-case basis. However, convincing evidence of their efficacy in severe disease from clinical trials is not yet available.

We also suggest that the assessment of symptoms in patients with sarcoidosis should involve the judicious use of objective testing such as pulmonary function tests and chest imaging to avoid unnecessary evaluations in the clinic and hospital. Again, this approach is a standard practice that we emphasize during this pandemic. The correlations between flares of sarcoidosis and changes in pulmonary function and chest imaging are known to be poor, and the determination of whether a patient with sarcoidosis is developing worsening disease may often be made on clinical grounds alone.

Conclusions

The management of sarcoidosis during the current COVID-19 pandemic poses many challenges for treating physicians. The present article offers a generalized approach to this issue (Fig 1). The risk of a poor outcome from COVID-19 infection must be factored into the clinician's treatment algorithm. This may result in an adjustment of the immunosuppressive regimen of the patient with sarcoidosis depending on the stability of his or her disease and consequences of disease reactivation. If immunosuppression is reduced, a clear-cut plan to monitor and treat exacerbations of sarcoidosis should be in place. We acknowledge that our understanding of COVID-19 infection is currently meager, and we expect that more evidence-based recommendations will be developed over time. Treating physicians should remain vigilant in their decision-making to the changing landscape of the available COVID-19 testing, the high variability in local and regional prevalence of the virus, and the evolving COVID-19 treatments.

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