COVID-19 infection in patients with sarcoidosis: susceptibility and clinical outcomes

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Purpose of review
Patients with sarcoidosis may be at higher risk of coronavirus disease-19 (COVID-19) as over 90% of the patients have pulmonary involvement and many are treated with immunosuppressive agents. This review will summarize the current literature regarding sarcoidosis and COVID-19, with a particular focus on susceptibility, clinical outcomes, management, and approach to vaccination.

Recent findings
Data about COVID-19 and sarcoidosis include a number of case series and reports, cohort studies, and registries. Literature is not conclusive whether patients with sarcoidosis have increased susceptibility to COVID-19. Patients with moderate to severe impaired pulmonary function may be at increased risk of adverse outcomes and mortality. Whether immunosuppressive medication increases risk of COVID-19 severity or affects vaccination response is not yet clear. Novel approaches, such as telemedicine and home monitoring programs, are promising to ensure continuity of care for patients with sarcoidosis during the COVID-19 pandemic.

Summary
Current evidence about the risk and clinical outcomes of COVID-19 infection in patients with sarcoidosis, is mainly extrapolated from other immune-mediated diseases. Hence, further research that focuses on the sarcoidosis population is warranted.

Keywords
coronavirus disease-19, immunosuppression, management, sarcoidosis, vaccination

INTRODUCTION
Sarcoidosis is a systemic inflammatory disease, caused by an unidentified trigger, leading to an inflammatory response, cytokine release and granuloma formation [1]. These granulomas are commonly found in the lungs, with 90% of patients having pulmonary manifestations of disease [1,2]. Patients with sarcoidosis may be at higher risk of contracting coronavirus disease-19 (COVID-19) and worse clinical outcomes due to pulmonary involvement, comorbidities, and the use of immunosuppressive medication. In this review, we strive to answer clinical questions to provide guidance to improve care for patients with sarcoidosis during the COVID-19 pandemic. We will discuss susceptibility and risk of adverse COVID-19 outcomes in patients with sarcoidosis, with a particular focus on immunosuppressive therapy. Subsequently, we will elaborate on the management and optimal monitoring of patients with sarcoidosis during the COVID-19 pandemic. Finally, we will touch on the management of COVID-19 as well as approach to vaccination in patients with sarcoidosis.

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SARCIOIDOSIS?

PATHWAYS IN THE IMMUNE RESPONSE

ARE THERE SIMILAR CELLULAR PATHWAYS IN THE IMMUNE RESPONSE IN CORONAVIRUS DISEASE-19 AND SARCOIDOSIS?

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 enters the cell by binding to the angiotensin-converting enzyme 2 receptor in the nasopharynx, oropharynx and lungs, leading to a viral inflammatory response [3]. The majority of patients who develop COVID-19 experience mild to moderate symptoms, whereas a small subset of patients experience severe manifestations of disease such as acute respiratory distress syndrome and multiorgan failure. The latter is thought to be due to an unattenuated hyperinflammatory response, a phenomenon known as cytokine storm syndrome [4]. The inflammatory cascade begins with viral RNA binding to pattern recognition receptors as the virus enters a cell of the innate immune system. Upon activation of these receptors, a series of events triggers the secretion of pro-inflammatory cytokines including tumor necrose factor (TNF)-alpha, interleukin (IL)-6, IL-1, IL-18, but most importantly interferon (IFN). This flood of cytokines can induce effector T-cell responses as well as recruit other immune cells to propagate further inflammation. Treatment for severe COVID-19 aims to target steps in this inflammatory cascade [5].

Sarcoidosis is thought to be caused by exposure to an unidentified antigen which leads to an inflammatory response in predisposed individuals. Contact with an antigen activates T lymphocytes, macrophages and antigen-presenting dendritic cells and leads to release of pro-inflammatory cytokines [1]. These pro-inflammatory cytokines play an important role in T-cell differentiation. Although sarcoidosis was once considered a typical Th1 disease with several Th1 cytokines found in bronchoalveolar lavage fluid cells, recently, Th17 and Th17.1 cells were found to correlate with prognosis [6,7]. Several of the cytokines involved in T-cell proliferation and differentiation signal through the Janus Kinase (JAK)-signal transducer and activator of transcription (STAT) pathway [1]. Other important cytokines contributing to granuloma formation and maintenance are IFN gamma and TNF alpha [1].

There may be some similarities in the pathogenesis of COVID and sarcoidosis. First of all, there is some overlap in cytokines involved, such as IL-6, IL-18 and TNF-alpha. Similarly, the JAK-STAT pathway is an important mediator in the immune response in sarcoidosis as well as in COVID-19 [1,5]. Interestingly, inhibition of the JAK-STAT pathway has been proposed as therapy for both refractory sarcoidosis and severe COVID-19 [8–10]. Whether potential similarities in pathogenesis of the two diseases leads to an increased – or decreased – risk of severe COVID-19 infection in patients with sarcoidosis requires further study.

IS THERE AN INCREASED SUSCEPTIBILITY OF CORONAVIRUS DISEASE-19 IN PATIENTS WITH SARCOIDOSIS?

Although our understanding of the pathophysiology of COVID-19 has vastly improved since the start of the pandemic, little is still known regarding how sarcoidosis impacts susceptibility to COVID-19 infection. Patients with sarcoidosis may have lymphopenia and suppression of the peripheral immune response at baseline, increasing susceptibility to infection [11]. Additionally, the use of immunosuppressive medication increases the risk of opportunistic infections, but whether this also applies for COVID-19 needs to be elucidated [12]. Baughman et al. conducted a survey study in 5200 patients with sarcoidosis, of whom 116 patients reported COVID-19 infection and 18 required hospitalization [13**]. The rate of COVID-19 in this cohort was 2.23% or 22,308 cases per million from April to July 2020. This was notably higher than the rate of COVID-19 in the general US population, which was 1,060 cases per million during the same time period. However, a subgroup analysis comparing patients with sarcoidosis to patients without sarcoidosis in the same geographic area found that rates of infection were similar between both groups. In the same study, the presence of pulmonary sarcoidosis and neurosarcoidosis were identified as

KEY POINTS

- There is limited data currently available to determine if patients with sarcoidosis are at increased risk of contracting COVID-19.
- Patients with sarcoidosis with impaired pulmonary function may be at increased risk of adverse COVID-19 outcomes.
- Rituximab may increase the risk of COVID-19 severity, although there is no conclusive evidence whether other immunosuppressive medications have a similar effect.
- Home monitoring programs can be useful to maintain the usual standard of care during the COVID-19 pandemic and to monitor patients with sarcoidosis and COVID-19 in the outpatient setting.
- It is recommended to offer COVID-19 vaccination to patients with sarcoidosis; the ACR offers guidance regarding approach to COVID-19 vaccination and the use of immunosuppressive medication.
factors that increased risk of COVID-19. Also, rituximab was associated with an increased risk of contracting COVID-19, whereas other immunosuppressive therapy was not. Interestingly, the presence of diabetes, hypertension, heart disease, or chronic obstructive pulmonary disease were not associated with increased risk of COVID-19 in this cohort. However, the authors rightly remark that the study was underpowered to detect small but significant changes due to low number of cases of COVID-19 in the cohort. At this point in time, it is unclear whether patients with sarcoidosis are at increased risk of COVID-19.

IS THERE INCREASED RISK FOR SEVERE DISEASE OR POOR OUTCOMES OF CORONAVIRUS DISEASE-19 IN PATIENTS WITH SARCOIDOSIS?

There are several factors that may increase the risk of adverse COVID-19 outcomes in sarcoidosis, which we define in this review as intubation or in-hospital mortality. Sarcoidosis affects the lung in most patients and can result in diminished pulmonary reserve in the form of obstructive or restrictive lung disease [2,14]. Multiple meta-analyses have found that respiratory diseases, especially COPD, are associated with increased risk of severe COVID-19 [15,16]. Several studies have shown that patients with interstitial lung disease (ILD) who contract COVID-19 were more likely to require hospital admission or ICU level care and had increased mortality rates, especially those with pulmonary fibrosis [17*,18,19]. Indeed, Morgenthal et al. found that the presence of moderately to severely decreased pulmonary function in patients with sarcoidosis is associated with increased rate of adverse COVID-19 outcomes [20**]. Additionally, comorbid conditions, such as hypertension and diabetes mellitus, that have been shown to be independently associated with increased mortality in COVID-19 are commonly seen in patients with sarcoidosis [15,16,21]. Overall, the current literature suggests that patients with sarcoidosis who contract COVID-19 may be at risk for worse outcomes. This highlights the need for close monitoring of patients with sarcoidosis and COVID-19. However, larger cohort studies are required to further characterize and quantify rates of severe COVID-19 outcomes in this population.

DO IMMUNOSUPPRESSIVE MEDICATIONS INFLUENCE THE DISEASE COURSE CORONAVIRUS DISEASE-19?

In general, immunosuppressive medications, especially glucocorticoids, increase the susceptibility to opportunistic infections [22,23]. This raises the question whether sarcoidosis patients treated with immunosuppressive medication are at higher risk of COVID-19 compared to patients not using such therapy. As data regarding clinical outcomes of COVID-19 in patients with sarcoidosis on immunosuppressive medication is scarce, we extrapolate outcomes from patients with other inflammatory rheumatic diseases. Table 1 highlights studies in which clinical outcomes of patients on immuno-suppressive therapy are described. Of note, these are all retrospective studies and registries, which prevents conclusions about causal relationships.

The most frequently used medication for sarcoidosis is prednisone. Patients taking less than 10 mg prednisone a day do not seem to be at higher risk for hospitalization or death from COVID-19 [24,25**]. Data are conflicting, however, regarding whether moderate to high dose glucocorticoids (equal to >10 mg prednisone/day) is associated with more severe outcomes. Two smaller retrospective studies did not find an association between prednisone >10 mg/day and an increased risk of hospitalization and mortality due to COVID-19. However, these studies may have been underpowered to detect small but significant effects [13**,17*]. Two large retrospective studies that used data from the ‘COVID-19 Global Rheumatology Alliance Provider Registries (C19-GRA)’ did demonstrate an association between prednisone >10 mg/day and higher risk of hospitalization and death from COVID-19 infection [25**,26]. As it stands, it is debatable whether moderate to high dose glucocorticoids are an independent risk factor for worse COVID-19 outcomes. Moderate to high dose prednisone is mainly prescribed in cases of severe sarcoidosis, suggesting the adverse outcomes might well be a reflection of sarcoidosis severity and activity. Remarkably, in the Recovery Trial (Randomized Evaluation of COVID-19 Therapy) dexamethasone decreased mortality among COVID-19 patients on oxygen or invasive mechanical ventilation [27*]. Consequently, dexamethasone is advised for all patients with COVID-19 requiring additional respiratory support, including those with sarcoidosis [28]. Other disease modifying antirheumatic drugs (DMARD) are methotrexate, azathioprine, myco-phenolate and leflunomide. For these DMARDs, no conclusions can be drawn with regard to the risk of severe COVID-19 due to limited data [13**,25**,26,29]. Interestingly, in an earlier analysis of the C19-GRA, Gianfrancesco and colleagues found that the use of anti-TNF treatment was associated with a lower risk of hospitalization [26,30]. It was speculated that this might be related to positive effect of anti-TNF treatment during the inflammatory phase of COVID-19 infection. In a later analysis of the C19-GRA which included a larger
Table 1. Immun suppressive therapy and outcomes of COVID-19 infection in patients with sarcoidosis, interstitial lung disease and rheumatic diseases

| Author          | Design                          | Number of patients | Immunosuppressive therapy                                                                                     | Outcome                                                                 |
|-----------------|---------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Baughman et al. 2020 [13**] | Self-reporting questionnaire on the risk and outcome of COVID-19 infection in patients with sarcoidosis | 5200 patients with sarcoidosis - 116 patients reporting COVID-19 infection - 18 required hospitalization | Data available of 105 patients of the 116 COVID positive patients - Prednisone < 10 mg (n = 57) - Prednisone > 10 mg (n = 15) - DMARDS: Methotrexate, azathioprine, mycophenolate, leflunomide (n = 24) - Hydroxychloroquine (n = 8) - Anti-TNF: infliximab, adalimumab (n = 7) - Rituximab (n = 7) | - Incidence of COVID-19 was 2.23% - 15.8% of the patients with COVID-19 required hospitalization - Pulmonary sarcoidosis, neurosarcoidosis and rituximab were associated with increased risk of contracting COVID-19 infection - Immunosuppressive therapy was not associated with increased risk of hospitalization |
| Morgenthau et al. 2020 [20**] | Retrospective cohort study | 7337 patients with COVID-19 infection - 37 patients with sarcoidosis | Data available of 37 patients with sarcoidosis and COVID-19 infections - Glucocorticoids (n = 11) - Non-Steroid Systemic Anti-Inflammatory Medications: Methotrexate, Azathioprine, Mycophenolate, Infliximab, Hydroxychloroquine (n = 14) - No therapy (n = 18) | - No significant association between sarcoidosis and adverse outcome (intubation/mechanical ventilation/mortality compared to the entire cohort) - Risk on adverse outcome was increased in patients with moderate/severe impairment in pulmonary function (OR = 7.8) |
| Jeny et al. 2020 [33] | Retrospective cohort study in 15 French centers | 36 patients with sarcoidosis admitted with COVID-19 infection | Data available of 36 patients with sarcoidosis admitted with COVID-19 - Glucocorticoids (n = 25) - Methotrexate (n = 8) - Mycophenolate (n = 3) - Azathioprine (n = 3) - Anti-TNF (n = 6) | - 36% of the admitted patients required intensive care support - Mortality rate was 14% - High prevalence of chronic comorbidities in the study cohort (33% diabetes, 39% hypertension, 33% lung fibrosis) |
| Galley et al. 2020 [19] | Retrospective cohort study | 123 ILD patients with COVID-19 - 16 patients with sarcoidosis | Data available of 123 ILD patients with COVID-19 - Glucocorticoids (n = 47) - Immunosuppressive drugs (n = 45) - No immunosuppressive medication (n = 31) | Prednisone and immunosuppressive therapy were not associated with an increased mortality rate |
| Giafrancesco et al. 2020 [26] | COVID-19 Global Rheumatology Alliance physician-reported registry | 600 individuals with rheumatic disease and COVID-19 - 10 patients with sarcoidosis | Data available of 600 patients with rheumatic disease and COVID-19 - Prednisone 1-9mg/day (n = 125) - Prednisone >10mg/day (n = 64) - No corticosteroids (n = 403) - csDMARD only, including antimalarial therapy (n = 272) - b/tsDMARDs only (n = 107) | - Prednisone 1-9mg/day was not associated with an increased risk of hospitalization - Prednisone >10mg/day was associated with higher risk of hospitalization compared to no prednisone use (OR = 2.05) - Other immunosuppressive medications were not associated with an increase the risk of hospitalization (OR = 1.23, P = 0.48) - Anti-TNF was associated with lower odds (OR = 0.4) of hospitalization compared to no Anti-TNF |
| Author          | Design                                      | Number of patients                      | Immunosuppressive therapy                                                                 | Outcome                                                                 |
|-----------------|---------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Drake et al. 2020 [17*] | International multicenter audit of patients with ILD admitted with COVID-19 | 161 ILD patients with COVID-19 infection matched with 322 non-ILD patients with COVID-19 infection, 9 patients with sarcoidosis | Data available of 161 ILD patients with COVID-19: Methotrexate/azathioprine (n = 5), Mycophenolate (n = 17), Corticosteroids (n = 45), No immunosuppressive therapy or antifibrotic medication (n = 106) | - Mortality ILD cohort 49% compared to matched cohort 35% without ILD  
- Mortality 50% in ILD cohort (n = 106) without medication  
- Mortality 51% in patients with prednisone (n = 45)  
- Patients with impaired lung function and obesity had an increased risk of death from COVID-19 |
| Esposito et al. 20 [18] | Case-control study | 46 ILD patients with COVID-19 were matched with 92 non-ILD patients. Number of patients with sarcoidosis unknown | Data available of 46 ILD patients with COVID-19: Corticosteroids (n = 11), Other immunosuppression (n = 18), No treatment (n = 17) | - Increased mortality in patients with ILD (OR 4.3)  
- Chronic corticosteroids or other immunosuppressive therapy use was not associated with death. |
| Strangfeld et al. 2021 [25**] | COVID-19 Global Rheumatology Alliance physician-reported registry | 3729 individuals with rheumatic disease and COVID-19. Number of patients with sarcoidosis unknown | Data available of 3729 patient with rheumatic diseases and COVID-19: Corticosteroids 1-10mg/dag (n = 983), Corticosteroids >10mg/dag (n = 220), csDMARDS monotherapy (n = 651), combination therapy (n = 753), Immunosuppressive (azathioprine, cyclophosphamide, ciclosporin, mycophenolate or tacrolimus) monotherapy (n = 175), combination therapy (n = 168), Anti-TNF monotherapy (n = 447), combination therapy (n = 357), Rituximab monotherapy (n = 91), combination therapy (n = 102) | - Prednisone >10mg/day was associated with increased mortality (OR 1.69) compared with no prednisone use  
- Rituximab, sulfasalazine, and immunosuppressive therapy were associated with increased mortality compared with methotrexate monotherapy  
- Chronic lung disease and moderate to high disease activity were associated with increased mortality. |

Anti-TNF, antitumor necrosis factor; bDMARDS, biological DMARDS; csDMARDS, conventional synthetic DMARDS; DMARDS, Disease-modifying antirheumatic drugs; tsDMARDS, targeted synthetic DMARDS.  
*aData are shown of selected number of immunosuppressive agents, that are frequently used as treatment for sarcoidosis.
cohort of patients, Strangfeld et al. did not find a positive effect of anti-TNF on mortality. Studies on B-cell therapy show that rituximab use was associated with more severe COVID-19 outcomes [25**,31]. It is suggested that this could be related to B-cell depletion, which can potentially compromise antiviral immunity and the development of SARS-CoV-2 antibodies [32]. This association, however, may also be influenced by the usual co-administration of methylprednisolone with rituximab [25**]. Overall, rituximab seems to increase the risk of severe COVID-19, whereas there is no conclusive evidence whether other immunosuppressive medications increase the risk of COVID-19 severity.

**HOW SHOULD SARCOIDOSIS BE MANAGED DURING THE CORONAVIRUS DISEASE-19 PANDEMIC?**

Early in the COVID-19 pandemic and in the absence of specific data, clinical recommendations on the use of immunosuppressive medication in sarcoidosis were provided. These advised to adjust treatments by prescribing immunosuppressive medication with caution, minimizing dosages or prolonging intervals between dosages if the clinical situation permitted [33]. One year later, there is still no conclusive evidence whether immunosuppressive medication increases COVID-19 severity. In general, the European League Against Rheumatism (EULAR) recommends no medication adjustments for patients with sarcoidosis during the COVID-19 pandemic [28].

Since sarcoidosis is a heterogenic disease, treatment regimens are often personalized for individual patients. It is essential to frequently assess the risk-benefit ratio of immunosuppressive medication, especially during the COVID-19 pandemic. The potential benefits of treatment with immunosuppressive medication should be weighed against the risk of under treatment and subsequent organ damage, whereas considering the risks and side-effects of medication. Notably, uncontrolled inflammatory or autoimmune disease has been associated with increased COVID-19 mortality, which highlights the importance of adequate disease control [25**].

**HOW SHOULD WE TREAT CORONAVIRUS DISEASE-19 IN PATIENTS WITH SARCOIDOSIS?**

Since the beginning of the pandemic, there have been a number of case series and reports that have sought to describe the clinical courses and treatment of COVID-19 in sarcoidosis patients. The literature reveals seven case series and reports, which include a total of 46 sarcoidosis patients who contracted COVID-19 [34–40]. Management of COVID-19 in these cases varied and consisted of treatments that are currently not recommended for treatment of COVID-19, such as various antivirals and antimalarials. Given the small number of cases and the heterogeneity of treatments, it is difficult to draw conclusions from the current literature on the optimal management of COVID-19 in specifically in sarcoidosis. In the United States, the current mainstay of treatment in the general population requiring hospitalization and supplemental oxygen are dexamethasone with or without the antiviral agent remdesivir [41]. On the other hand, the European Respiratory Society advises against the use of remdesivir in hospitalized patients and recommends only dexamethasone and tocilizumab in addition to supportive management [42]. Although these guidelines are also used for sarcoidosis patients, an additional consideration that must be made is continuation or modification of immunosuppressive regimens. The EULAR guidelines advise to continue chronic corticosteroids during COVID-19 infection [28]. The decision to continue or withdraw other chronic immunosuppressive medication during acute COVID-19 requires an assessment of the risk-benefit ratio and should be individualized with each patient. Fortunately, the vast majority of patients with sarcoidosis and COVID-19 will not require hospital admission and supplemental oxygen and can be managed with self-monitoring at home.

**HOW TO MONITOR SARCOIDOSIS PATIENTS DURING THE CORONAVIRUS DISEASE-19 PANDEMIC?**

The COVID-19 pandemic has limited access to the hospital and threatened the continuity of care within our healthcare systems. Many follow-up visits are now conducted via telephone or video consultation. This may lead to suboptimal discussions, outcome assessment, and potential delays in treatment decisions. Innovative approaches in dailycare, such as home monitoring programs including home spirometry have increasingly been used in the past year [43,44]. Portable electronic spirometers have proved to accurately measure forced vital capacity at home in patients with ILD [45,46]. Home spirometry may allow for early detection of deterioration of lung function and guide treatment decisions [6]. Measurement of diffusion capacity is more challenging, but surrogate measures are currently being explored. Recent data suggest a one-minute sit-to-stand test may give an indication of gas exchange impairment and diffusion capacity, but this is not yet validated [47]. Virtual platforms also enable collection of patient-reported comorbidities, symptoms, and side-effects of medication as well as...
capturing self-measured data by patients, including blood glucose, blood pressure, and weight. Thus, these novel approaches can be useful to maintain the usual standard of care and continue clinical research for patients with sarcoidosis during and beyond the COVID-19 pandemic [48]. Furthermore, home monitoring may improve patient insight into their disease while at the same time empowering patient education and self-management. Home monitoring can also be of great value to closely monitor patients with COVID-19 infection in the outpatient setting, especially for patients with underlying chronic diseases that are at risk for severe COVID-19 disease. Several home monitoring programs for COVID-19 patients have been developed. These programs have demonstrated safety and efficacy in detecting worsening of symptoms while maintaining high patient satisfaction [49–51,52*].

A pilot study demonstrated that home monitoring reduced mean duration of hospitalization, especially in patients requiring oxygen support at discharge while being cost-effective [52*]. Overall, if available, we recommend the use of home monitoring, self-reporting of symptoms and oxygen saturation in patients with sarcoidosis and COVID-19 infection.

WHAT DO WE KNOW ABOUT THE VACCINATION RESPONSE IN SARCOIDOSIS?

Currently, there are no data about COVID-19 vaccination in patients with sarcoidosis. Previous data regarding vaccination in sarcoidosis is limited and conflicting. Seyhan et al. conducted a small case-control trial in which the tetanus vaccine was administered to 48 sarcoidosis patients and 33 healthy controls. They found that 50% of the sarcoidosis patients, compared to 23% of healthy controls, did not mount an adequate antibody response to vaccination [53]. On the other hand, in another case-control trial, Tavana et al. showed that flu vaccination is safe in sarcoidosis and that sarcoidosis patients mounted an adequate antibody response to vaccination compared to healthy controls [54]. Both aforementioned studies, however, are limited by small sample sizes and fail to account for concurrent use of immunosuppression.

As immunosuppressive medications are the mainstay of treatment for sarcoidosis, it is important to consider how these agents will impact the response to vaccination. Although there is a paucity of data in sarcoidosis, this issue has been studied in rheumatoid arthritis (RA). Immunogenicity of the flu vaccine has been shown to be adequate in RA patients on glucocorticoids [55,56]. On the other hand, a study of Fisher et al. showed insufficient antibody response in patients using prednisone doses higher than 10 mg a day [57]. Studies have shown that methotrexate and TNF-alpha inhibitors may dampen the immunogenicity of the influenza vaccination compared to healthy controls, RA patients still produced adequate levels of antibodies [55,58]. Conversely, RA patients on B-cell depleting therapy demonstrate a decreased antibody response to influenza vaccination [58–60], although this effect may be mitigated by administering the vaccine at least 6 months after the last dose of therapy [60,61]. In summary, data in RA demonstrates that some agents diminish the production of antibodies after vaccination, the relationship between antibody titers and protection from infection is not straightforward as other factors may be more important, such as efficacy of neutralizing antibodies, in

| ACR, 2021 [62**] | Soy et al. 2021 [63] |
|------------------|---------------------|
| **Prednisone**   |                     |
| Low dose prednisone (<20mg/day): do not delay vaccination. |
| High dose prednisone (>20mg/day): no consensus was reached. |
| COVID-19 vaccination should be given in patients receiving prednisone <10mg/day. |
| **Methotrexate** |                     |
| Do not delay vaccination. Skip 1 dose of methotrexate after vaccination. |
| In stable patient skip 1 dose of methotrexate before and 1 dose after vaccination. |
| **TNF alpha inhibitors** |                 |
| Do not delay vaccination. No modification in TNF alpha treatment is needed. |
| TNF alpha inhibitors do not seem to have an impact on the effect of vaccination. Consider a safety margin of 14 days before and after administration of the vaccine in clinical stable patients. |
| **Rituximab**    |                     |
| Vaccination around 4 weeks before the next rituximab cycle. |
| Vaccination at least 4 weeks before or 6 months after rituximab is received. |

TNF, tumor necrosis factor.

*Both reviews remark that their recommendations are based on extrapolation from other vaccine studies and may change when data on COVID-vaccination in patients with rheumatic diseases become available.
determining protection from infection. Vaccination of sarcoidosis patients against COVID-19 is currently recommended [62**]. The American College of Rheumatology (ACR) has provided guidance related to the use of immunosuppressive medications during COVID-19 vaccination [62**]. Soy et al. prepared a practical approach to the use of immunosuppressive medications during COVID-19 vaccination in rheumatic diseases [63]. Table 2 shows the recommendations of the ACR and of Soy et al.

A recent study investigated the immunogenicity of COVID-19 vaccination in patients with immune-mediated inflammatory diseases (IMID) in two independent cohorts [64]. The first cohort consisted of 51 patients with IMID, 25 patients were using methotrexate and 26 patients were using anticytotoxic and/or other immunomodulators. These patients were compared with 26 healthy controls. The second cohort consisted of 182 healthy individuals, 20 patients with IMID on methotrexate monotherapy and 11 patients treated with TNF alpha inhibitors. In both cohorts, immunogenicity was decreased in patients with IMID who were using methotrexate therapy. Combined analyses showed adequate response in over 90% of the healthy subjects and patients with IMID on biological treatment and only in 62.2% of the patients with IMID on methotrexate-ate. Further studies are needed to confirm this finding and to evaluate if additional doses of vaccine or modification of methotrexate treatment is needed [64].

CONCLUSION

The COVID-19 pandemic has presented a challenge to clinicians caring for patients with sarcoidosis. Close monitoring of these patients is necessary as they may be at increased risk for worse COVID-19 outcomes compared to the general population, but is also complicated due to a decrease in hospital visits and pulmonary function test capacity. Home monitoring can be of great value to monitor patients and guide treatment decisions. As clinicians, we must be mindful of each patient’s immunosuppressive regimen and continually assess the risk-benefit ratio of adjusting these medications. To provide further protection against disease, it is also advised to vaccinate sarcoidosis patients against COVID-19. International collaboration and large prospective patient registries could help to better understand COVID-19 outcomes in sarcoidosis in the near future.

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Conflicts of interest

There are no conflicts of interest.

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This study surveyed a total of 5200 sarcoidosis patients, of which 116 contracted COVID-19. The authors found that the rate of COVID-19 in sarcoidosis and non-sarcoidosis patients were similar.

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