



# State-of-the-Art Treatments for Sarcoidosis

REVIEW

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## ABSTRACT

Sarcoidosis is a heterogeneous disease with various treatment indications. Although it affects mainly the lungs, sarcoidosis can affect every organ, especially when the disease course is chronic and protracted. Regular patient follow-up is recommended for early recognition of active, ongoing organ-specific granulomatous inflammation to avoid progression to irreversible fibrosis. In this review, we elaborate on treatment indications and various anti-sarcoidosis regimens proven useful in clinical trials. We also review specialized treatment of specific disease manifestations, with a focus on cardiac sarcoidosis. We also report on treatment for special conditions such as fatigue and small fiber neuropathy. Treatment for sarcoidosis is an emerging landscape, with new data complementing the existing knowledge.

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KEYWORDS:

sarcoidosis treatment;  
cardiac sarcoidosis; advanced  
sarcoidosis; neurosarcoidosis

TO CITE THIS ARTICLE:

Papanikolaou IC, Antonakis  
E, Pandi A. State-of-the-Art  
Treatments for Sarcoidosis.  
Methodist DeBaKey Cardiovasc  
J. 2022;18(2):94-105. doi:  
10.14797/mdcvj.1068

## INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease of yet unknown etiology. It has great predilection for the lungs, but multiorgan involvement is common, especially when the disease course is chronic and protracted. Timely recognition and treatment is important as inflammation may progress to fibrosis, leading to irreversible organ damage. Older as well as recent guidelines for follow-up include identification of symptoms, history and physical examination, pulmonary function testing, and blood tests (complete blood counts, serum creatinine, serum alkaline phosphatase, serum calcium).<sup>1,2</sup> Depending on symptoms, additional tests may include an eye examination, cardiac investigations, vitamin D assessment, and computed tomography (CT) of the lungs. Cardiac sarcoidosis (CS) occurs in 5% of all sarcoidosis cases, but autopsy and imaging studies reveal clinically silent CS in 25% of cases in the United States.<sup>3</sup> CS manifests with atrioventricular blocks, arrhythmias, heart failure, and sudden cardiac death, accounting for up to 25% of total sarcoidosis deaths; therefore, prompt recognition and treatment is crucial.<sup>4</sup> CS affects all races, has a mean age presentation of 50 years, and may be isolated without evidence of extracardiac sarcoidosis in 25% of those who have it.<sup>4</sup> In this review, we address the principles and indications of sarcoidosis treatment, regimens and disease-modifying drugs, and treatment of special conditions.

## INDICATIONS FOR TREATMENT

Not all sarcoidosis patients need systemic immunomodulatory treatment. This variation occurs because in roughly 30% of cases, the disease may subside by itself without ever being treated.<sup>5</sup> Also, certain disease manifestations (ie, anterior uveitis, skin disease other than lupus pernio) may be treated only locally. Conversely, a recent British Thoracic Society report states that a significant proportion, up to 30%, of patients develop severe and worsening chronic disease requiring ongoing systemic treatment. Mortality is significant among this subgroup of patients, ranging up to 25%.<sup>6</sup>

The decision to treat with disease-modifying agents requires symptomatic, ongoing, and gradually worsening organ involvement (pulmonary or extrapulmonary) as well as certain asymptomatic but significant extrapulmonary manifestations, namely CS, neurosarcoidosis, posterior uveitis, and hypercalcemia.<sup>1,2</sup> In other words, treatment is warranted when there is danger of permanent debilitating organ damage or dysfunction with associated morbidity and/or a significantly compromised health-related quality of life

on patient-reported outcomes.<sup>6</sup> Thus, the goal of treatment is to prevent irreversible evolution of active granulomatous inflammation to fibrosis.<sup>7</sup> Disease activity has to be demonstrated before initiation of treatment because already established organ dysfunction should not be treated; disease activity is not sufficient by itself for treatment initiation when organ dysfunction is absent or mild.

Diagnosis of CS with high probability requires abnormal findings in electrocardiogram and/or Holter monitoring and/or echocardiography with abnormal advanced imaging features at cardiac magnetic resonance (CMR) and/or cardiac fluorodeoxyglucose positron emission tomography (FDG-PET).<sup>8,9</sup> Isolated CS may be diagnosed clinically in the absence of cardiac and extracardiac histology when positive PET scan combines with clinical features with or without positive CMR.<sup>8,10</sup>

Recent studies have identified key risk factors for increased mortality in pulmonary sarcoidosis, including decreased diffusion capacity of carbon monoxide (DLCO), presence of pulmonary fibrosis in high-resolution CT, and pulmonary hypertension.<sup>11,12</sup> The ideal regimen and medication doses in sarcoidosis are not always straightforward, because randomized double-blind placebo-controlled trials are generally lacking in sarcoidosis due to disease complexity, heterogeneity, and ethical considerations to withhold established treatments (with corticosteroids). **Table 1** summarizes a treatment algorithm of CS.<sup>13,14</sup> FDG-PET seems to be useful to monitor active myocardial inflammation.<sup>15</sup> Treatment has not shown to alter the natural course of the disease longitudinally, as granulomas often recur or progress. The most efficient drug against sarcoidosis is undisputedly corticosteroids. The other two categories of drugs with anti-inflammatory effect are antimetabolites and biologic agents.

## TREATMENTS CORTICOSTEROIDS

Corticosteroids remain the mainstay first-line treatment of sarcoidosis. They have been proven to improve overall disease control, symptoms, quality of life, and pulmonary radiology and/or delay disease deterioration in patients with symptomatic pulmonary sarcoidosis. These effects are short-term, lasting for a period of 1 to 2 years, and fade after treatment withdrawal.<sup>16-20</sup> Note that oral corticosteroids may not have an effect on pulmonary physiology as expressed by forced vital capacity (FVC) and diffusing capacity for carbon monoxide. Furthermore, inhaled corticosteroids, commonly used, have proven ineffective in clinical trials.<sup>21</sup>

Studies show that an initiating dose of prednisone at 20 mg daily is not inferior to higher doses in clinical

Monitoring	At least yearly or sooner depending on symptoms, disease severity, laboratory parameters (echocardiography, troponin, BNP)
Addressing concomitant cardiovascular risk factors	Coronary artery disease, hypertension
Standard medical treatments of heart failure, diastolic dysfunction	
Managing conduction abnormalities (AV blocks)	Consider pacemaker
Managing ventricular arrhythmias, risk for sudden cardiac death	Consider implantable cardioverter defibrillator
Immunosuppressive treatment*	Administer in functional cardiac abnormalities (arrhythmias, myocardial pathology, blocks)® In asymptomatic cases with normal ejection fraction: individualized assessment as per treatment initiation
First-line treatment: corticosteroids	Second-line treatment: methotrexate, leflunomide, azathioprine, mycophenolate mofetil Third-line treatment: infliximab, adalimumab, cyclophosphamide

**Table 1** Management of cardiac sarcoidosis.

\*Risk factors: Age greater than 50, left ventricular ejection fraction of less than 40%, New York Heart Association functional class 3 or 4, increased left ventricular end-diastolic diameter, late gadolinium enhancement on cardiac MRI, ventricular tachycardia, cardiac inflammation identified by fluorodeoxyglucose positron emission tomography (FDG-PET) scan, echocardiographic evidence of abnormal global longitudinal strain, interventricular septal thinning, elevated troponin or BNP. BNP: brain natriuretic peptide; AV: atrioventricular

®: Monitor myocardial inflammation with FDG-PET

efficacy, control of the disease, physiology, or quality of life parameters.<sup>22-24</sup> In recent studies, these relatively moderate doses are shown to manage sarcoidosis manifested as acute disease or as flares of chronic disease, and they are currently recommended by major societies (British Thoracic Society, European Respiratory Society) as an initiation dose with specific exceptions.<sup>6,14</sup> These guidelines consider the significant toxicity of treatment with corticosteroids associated with both cumulative dose and duration of treatment. Common side effects including weight gain, diabetes, glaucoma, osteoporosis, and depression have been frequently observed in sarcoidosis patients.<sup>25</sup>

When initiating corticosteroids in a patient with sarcoidosis, close follow-up every 3 months is mandatory. The initial dose is tapered after 3 to 6 weeks, usually by 5 mg, targeting a maintenance dose of 5 to 10 mg of prednisone by approximately 6 months after initiation of treatment. The maintenance dose is required by the majority of patients for a period of 6 to 24 months.

Based on existing literature, several principles apply when considering treating pulmonary sarcoidosis with corticosteroids: (1) acute disease and flares of chronic disease require the same prednisone doses, (2) the chronic maintenance dose should be the lowest possible, and (3) treatment with corticosteroids should be fairly prolonged to allow clearance of the etiologic antigen and adequate suppression of granulomatous reaction.<sup>7</sup>

Decision to discontinue corticosteroids is based on disease activity and end organ damage. When adequate control of the disease is accomplished, they should be

tapered off. Optimal duration of treatment is not known. Factors that may facilitate decisions in clinical practice are the appropriate selection of high-risk cases, PET-CT scan, and quality of life parameters. Up to 70% of patients experience sarcoidosis relapse during corticosteroids tapering or after treatment withdrawal. Relapses are treated with the same corticosteroid dose as in acute disease.

Addition of a second anti-inflammatory agent is deemed necessary when disease is severe and continued, when serial relapses occur, when corticosteroids are unable to be tapered below 10 to 15 mg of prednisone, when toxicity is significant, and when disease does not respond to corticosteroids.<sup>26</sup>

## METHOTREXATE

The most commonly studied second-line agent in sarcoidosis is antimetabolite methotrexate (MTX). MTX has exhibited a higher efficacy rate among second-line options managing disease control and steroids tapering in about 65% to 85% of patients with persistent pulmonary sarcoidosis.<sup>26-29</sup> MTX has also shown improvement in radiology and in FVC but only in observational or retrospective studies.<sup>26-29</sup> Additionally, MTX has proven effective in neurosarcoidosis, cardiac disease, skin, eye, and disrupted calcium metabolism.<sup>1</sup> It is given at a total dose of 15 mg weekly, divided in one or two doses. The most common side effects are blood (cytopenias) and liver toxicities, so these parameters should be monitored closely. To prevent bone marrow toxicity, concomitant treatment

with folic acid is imperative. Less than 10% of patients have to stop MTX because of toxicity, and relapses after MTX withdrawal may occur.<sup>28</sup> When initiating MTX, males and females of child-bearing age should be warned to prevent fertility due to fetal toxicity during pregnancy. Based on the existing evidence and acceptable toxicity profile, MTX is the recommended first option for a steroid-sparing second-line agent when treating sarcoidosis.<sup>14,26</sup>

### AZATHIOPRINE

Azathioprine (AZA) is a second antimetabolite that has long been used for rheumatic and hematologic diseases and historically has been used in sarcoidosis. Its efficacy is considered less than that of MTX, ranging between 20% to 80%.<sup>29,30</sup> However, these data come from retrospective or observational studies only. Additionally, AZA has significant side effects, mainly gastrointestinal issues, myelodysplasia, malignancies, and secondary infections, with treatment cessation more frequent than MTX. Recent European Respiratory Society (ERS) guidelines made no recommendation for its use as a steroid-sparing agent in sarcoidosis.<sup>14</sup>

### LEFLUNOMIDE

Leflunomide is a cytotoxic drug used in rheumatoid arthritis. Small series have shown efficacy of leflunomide at a dose of 10 to 20 mg daily in pulmonary and extrapulmonary sarcoidosis to improve pulmonary physiology, quality of life, extrapulmonary organ response, and as a steroid-sparing agent.<sup>31,32</sup> Leflunomide is typically used when a need arises for a second agent with a better safety toxicity profile than MTX. However, leflunomide has adverse effects, most significantly interstitial pneumonia and peripheral neuropathy.<sup>33,34</sup>

### HYDROXYCHLOROQUINE

Chloroquine and hydroxychloroquine (HCQ) are antimalaria drugs used to treat sarcoidosis. Recently, HCQ is used more often due to its lower toxicity profile, although retinopathy remains a significant concern, prompting ophthalmology evaluation upon symptoms.<sup>35</sup> HCQ has shown efficacy in cutaneous sarcoidosis and hypercalcemia.<sup>36,37</sup> In these conditions, it is usually given as an adjunct to low-dose corticosteroids or monotherapy. One randomized trial showed some efficacy in pulmonary sarcoidosis and physiology.<sup>38</sup> Considered less potent than MTX or other second-line agents, HCQ may be considered in refractory cases when drug toxicity is significant and in combination with one or two other drugs.

### MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is a powerful inhibitor of lymphocyte proliferation, used to prevent allograft rejection after transplant. Used in various rheumatic diseases, its

role in sarcoidosis remains unclear. Retrospective studies showed that MMF has a steroid-sparing effect in chronic sarcoidosis and neurosarcoidosis but is probably less effective than other second-line agents (mainly MTX), with higher relapse rates and a more favorable toxicity profile.<sup>39-41</sup> Its specific position in the treatment pyramid, likely as a second-line agent, must be further elucidated.

### INFLIXIMAB AND OTHER BIOLOGIC AGENTS

Anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) agents are considered effective third-line drugs in sarcoidosis (especially with refractory pulmonary disease and neurosarcoidosis) by blocking TNF- $\alpha$ , a significant cytokine in granulomatous inflammation. In particular, infliximab (and biosimilars) have shown improvement in FVC in two double-blind randomized studies and was granted a conditional recommendation for use in refractory pulmonary sarcoidosis under CS with or without a second-line agent.<sup>42,43</sup> Infliximab is further proven effective in lupus pernio (efficacy 77%), cutaneous sarcoidosis, and neurosarcoidosis (clinical improvement 77%, imaging improvement 82%).<sup>44,45</sup> Clinicians must be aware of side effects, ie, infections and tuberculosis.<sup>46,47</sup> Adalimumab may be an alternative in case of infliximab intolerance, as shown (at least partly) in small open-label studies.<sup>48</sup> Conversely, neither golimumab nor ustekinumab (anti-IL12/23) showed efficacy in refractory pulmonary sarcoidosis in one randomized trial.<sup>49</sup>

### OTHER TREATMENTS

Various other drugs have been tested in sarcoidosis. Phosphodiesterase inhibitors, pentoxifylline, roflumilast, and apremilast have shown to reduce disease flares, improve quality of life, and improve cutaneous disease, respectively, in small studies.<sup>50-52</sup> Rituximab is an anti-CD20 B-lymphocytes antibody that has shown partial efficacy in small case series of advanced pulmonary, eye, and neurosarcoidosis, with a favorable tolerance profile, and may be considered a third-line option.<sup>53</sup> Antimycobacterial treatment (CLEAR regimen) for 4 months failed to demonstrate clinical or physiological improvement in chronic pulmonary sarcoidosis.<sup>54</sup> Repository corticotropin injection (RCI) was approved in the 1950s for sarcoidosis. Originally considered a steroid analog, RCI may have additional immunological properties and a steroid-sparing effect, although its action is currently limited.<sup>55</sup> Janus kinase inhibitors are a drug family recently introduced in sarcoidosis treatment. Among them, tofacitinib showed 60% steroid-sparing efficacy in chronic sarcoidosis in a small proof-of-concept study.<sup>56</sup> An overview of drugs used, dosages, and respective monitoring events, with a focus on CS, is presented in [Table 2](#).

DRUG	DOSE	SIDE EFFECTS	CARDIAC SARCOIDOSIS
Prednisone	20 mg qd Follow-up 5-10 mg qd	Diabetes Weight gain Osteoporosis Glaucoma Cataract Depression/psychosis	Initiating dose 30 mg qd
Methotrexate	10-15 mg once a week	Nausea, bone marrow suppression, liver toxicity, pulmonary toxicity	Effective in combination with corticosteroids
Leflunomide	10-20 mg qd	Nausea, peripheral neuropathy, interstitial pneumonia	
Azathioprine	50-250 mg qd	Nausea, bone marrow suppression, liver toxicity, malignancies	Less effective than methotrexate
Mycophenolate mofetil	500-1500 mg bid	Diarrhea, monitor blood cell counts	Reasonably effective
Infliximab	3-5 mg/kg initially, 2nd dose after 2 weeks, then every 4-6 weeks	Tuberculosis activation, infections, contraindicated in severe heart failure, demyelinating neurological diseases, active tuberculosis, prior malignancy	Effective, caution for infections, cardiac symptoms <sup>47</sup>
Adalimumab	40 mg every 1-2 weeks	Tuberculosis activation, infections Contraindicated in severe heart failure, demyelinating neurological diseases, active tuberculosis, prior malignancy	Less effective than infliximab, caution for infections, cardiac symptoms <sup>47</sup>
Rituximab	500-1000 mg every 1-6 months	Screen for hepatitis, tuberculosis activation, humoral deficiency	
Hydroxychloroquine	200-400 mg qd	Retinopathy	

**Table 2** Drugs used to treat sarcoidosis. qd: every day; bid: twice a day

## SPECIFIC CONSIDERATIONS

### EXTRAPULMONARY SARCOIDOSIS

Depending on organ involvement, extrapulmonary sarcoidosis may warrant local treatment, systemic treatment escalation, or multimodality interventions.

#### Cutaneous Sarcoidosis

Cutaneous sarcoidosis should initially be treated with local or intralesional corticosteroid injection. Cosmetically important disfiguring lesions (such as lupus pernio) should be treated with oral corticosteroids to achieve control in two-thirds of cases.<sup>57</sup> Continued disease should be treated with an additional agent. Hydroxychloroquine and methotrexate are currently used and have shown efficacy in small studies.<sup>58</sup> Randomized studies provide support for the use of infliximab in severe skin disease.<sup>44,59</sup> Thalidomide, on the other hand, is proven ineffective compared with a placebo in skin sarcoidosis.<sup>60</sup>

#### Ocular Sarcoidosis

Anterior uveitis should be treated locally with steroidal eye drops. Posterior uveitis, however, carries risk for blindness and requires systemic treatment, which includes corticosteroids and/or methotrexate in the majority of

cases.<sup>61</sup> Mycophenolate mofetil and infliximab may be used as well, depending on course and individual toxicities.

#### Calcium Metabolism

Hypercalciuria is treated initially with dietary dairy and restricted sun exposure while hypercalcemia requires systemic treatment. Corticosteroids and/or HCQ are effective in treating hypercalcemia, the latter as sole treatment particularly in cases of unacceptable corticosteroids toxicity.<sup>36</sup> Osteoporosis should be treated carefully in sarcoidosis, as exogenous vitamin D supplementation may lead to hypercalcemia and is only indicated when 1,25(OH)<sub>2</sub> vitamin D levels are normal or reduced. When 1,25(OH)<sub>2</sub> vitamin D is elevated, osteoporosis is treated with bisphosphonates or denosumab.<sup>62</sup>

#### Cardiac Sarcoidosis

Treatment of CS is two-fold. First, based on current guidelines and cardiology consultation, patients at increased risk for sudden cardiac death should be recognized and given an implantable cardioverter defibrillator (ICD), as in all arrhythmogenic cardiomyopathies. Such patients include those with episode of arrest, left ventricle ejection fraction (LVEF) ≤ 35%, and sustained ventricular tachycardia but

also when LVEF is > 35% along with certain physiological or functional features.<sup>63-65</sup> When no indication for ICD exists, performing an electrophysiology study is reasonable. Anti-arrhythmic drugs, pacemaker placement in high A-V blocks, and catheter ablation have been of modest value.<sup>66</sup>

Second, patients with clinically relevant cardiac sarcoidosis should initiate anti-inflammatory treatment with corticosteroids. Studies have shown long-term benefit of early initiation of immunosuppressives in CS. Corticosteroids in particular have shown survival and functional benefit, albeit not in randomized trials; lower doses of prednisone (no more than 30 mg) are not inferior to higher doses and are preferred.<sup>67-70</sup> Ongoing studies are underway to evaluate prospectively the impact and dose of corticosteroids in CS (Cardiac Sarcoidosis Multi-center Cohort Study, NCT01477359). Regarding second- and third-line agents, functional benefit is shown with MTX, MMF, infliximab, and adalimumab.<sup>71-74</sup> In most of these studies, adding a second agent was superior to treatment with corticosteroids alone. Anti-TNF agents were not associated with heart failure deterioration in these studies of CS patients. Unanswered questions remain as per the duration of treatment, the value of adding a second agent from the beginning or later in the course of the disease as well as the management of clinically asymptomatic (ie, normal rhythm and ejection fraction) cardiac involvement.<sup>75</sup> FDG-PET seems a promising biomarker to serially evaluate cardiac inflammation and response to treatment.<sup>15</sup>

### Pulmonary Hypertension

Sarcoidosis-associated pulmonary hypertension (SAPH) is encountered in 5% to 20% of sarcoidosis patients. SAPH along with pulmonary fibrosis constitute an advanced sarcoidosis phenotype, ie, sarcoidosis with a risk of significant loss of organ function or death.<sup>76</sup> When SAPH is suspected, right heart catheterization is necessary for confirmation and differentiation of multiple SAPH etiologies (ie, left heart failure, precapillary PH, extrinsic compression, and pulmonary veno-occlusive disease). Precapillary SAPH carries a 3-year mortality of 30%. Worse outcomes relate to reduced DLCO < 35%, reduced 6-minute walk distance < 300 m, and preserved FEV1/FVC ratio.<sup>77</sup> In a small series, epoprostenol and combined ambrisentan with tadalafil showed hemodynamic and functional improvement.<sup>78,79</sup> As to randomized trials, bosentan improved pulmonary hemodynamics at 4 months of treatment, while riociguat significantly delayed time to clinical worsening and improved exercise capacity at 1 year of treatment.<sup>80,81</sup>

### Pulmonary Fibrosis

Pulmonary fibrosis extending > 20% of the lungs in high-resolution CT implies advanced disease with high mortality risk.<sup>11,12</sup> Transplant referral is indicated when sarcoidosis

progresses to respiratory failure despite treatment. Transplant has been performed in patients with fibrosis or obstructive or mixed defects with or without pulmonary hypertension. Ensuing 5-year survival rates were 69%, with age and fibrosis being the worst prognostic factors.<sup>82</sup>

Antifibrotic treatment with nintedanib in sarcoidosis with pulmonary fibrosis has shown to ameliorate vital capacity decline, as it did with other progressive fibrosing interstitial lung diseases, in the IN-BUILD trial and may be considered pretransplant.<sup>83</sup> A study exploring pirfenidone in fibrotic sarcoidosis is currently underway.

### Neurosarcoidosis

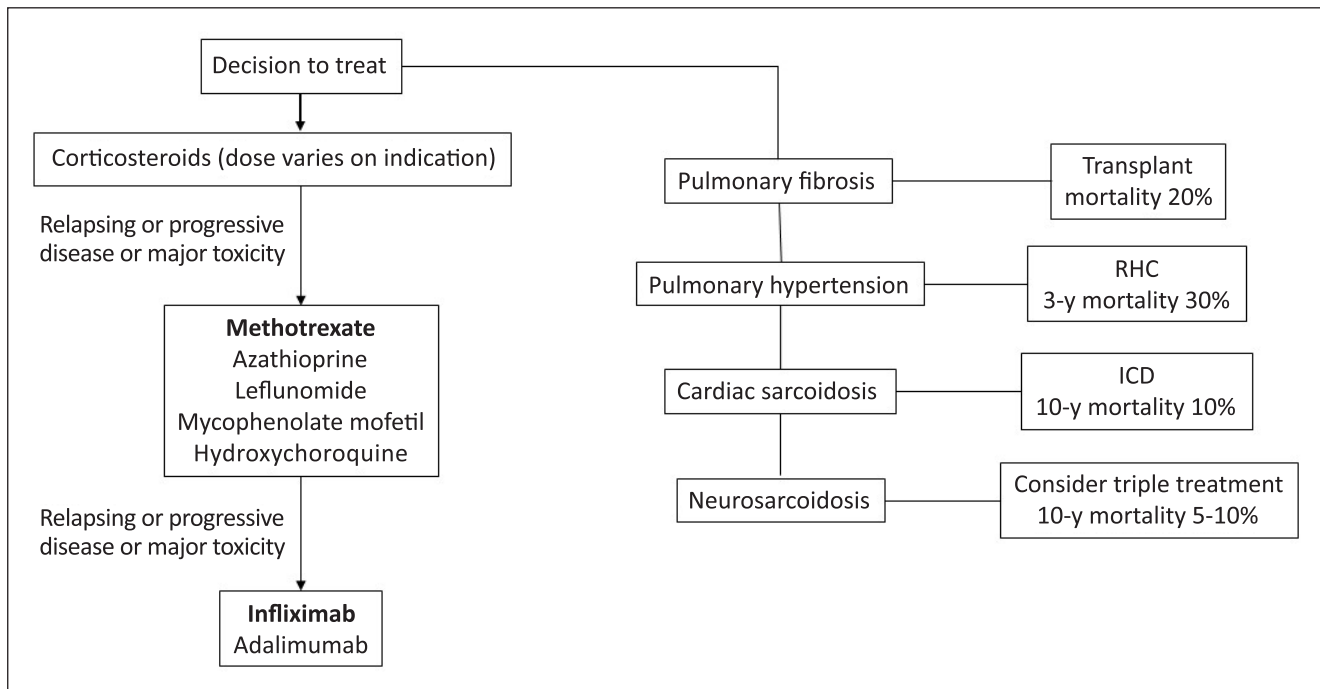
Occurring in 5% to 20% of sarcoidosis, neurosarcoidosis manifests mainly as cranial nerve palsy, parenchymal masses, hydrocephalus, or aseptic meningitis and is associated with a 10-year mortality of 5% to 10%.<sup>84,85</sup> Although data are derived from retrospective studies and meta-analyses, they support initiation of corticosteroids versus no treatment, with efficacy rates of corticosteroids alone up to 70%.<sup>84,85</sup> The dose usually administered in clinical practice is prednisone  $\geq$  0.5 mg/kg daily. A second-line agent will probably be required in continued or relapsing disease, with MTX exhibiting superiority versus MMF, azathioprine, and HCQ (response in 55-70% of cases).<sup>84,86</sup> Lastly, about a third of patients with neurosarcoidosis may require a third-line agent concomitantly. Infliximab is mostly efficient as shown in two studies and less toxic than cyclophosphamide, but relapses tend to occur after treatment discontinuation.<sup>45,87</sup>

**Figure 1** depicts lines of treatment with available regimens and, on the right-hand side, specific considerations in advanced disease.

### FATIGUE

Fatigue affects  $\geq$  60% of patients with sarcoidosis, compromising quality of life, yet it is not directly related to disease activity of the granulomas. Fatigue may be multifactorial due to diabetes, thyroid disease, sleep apnea, depression, and neuropathies. Interventions to alleviate fatigue include pulmonary rehabilitation, neurostimulants, and low-dose corticosteroids. Pulmonary rehabilitation has shown in several studies to improve physical activity, exercise capacity, or just the levels of fatigue.<sup>87,88</sup> Inspiratory muscle training, a component of pulmonary rehabilitation, may add benefit.<sup>89</sup> Pulmonary rehabilitation should be offered in sarcoidosis, as with all interstitial lung diseases. Dexmethylphenidate hydrochloride and armodafinil improved fatigue in 10 and 15 patients with sarcoidosis, respectively, but their use is restricted by side effects such as insomnia and anxiety.<sup>90,91</sup> Lastly, in a randomized trial of sarcoidosis subjects without indication





**Figure 1** Schema for sarcoidosis treatment. Systemic treatment initiates regularly with corticosteroids, with dose depending on indication. Among second- and third-line treatments, methotrexate and infliximab (in bold) have the most evidence for use. Agent selection depends on indication, comorbidities, and anticipated toxicity. A proportion of these patients develop features of advanced sarcoidosis (right column) with respective mortality risk where additional treatment modalities may be required. RHC: right heart catheterization; ICD: implantable cardioverter defibrillator<sup>14,69,76,81,83,84</sup>

for immunosuppressant treatment, 1 mg dexamethasone daily for 12 months improved fatigue parameters along with serum inflammatory markers; however, this intervention needs confirmation.<sup>92</sup>

### SMALL FIBER NEUROPATHY

Small fiber neuropathy relates to many diseases, is characterized by debilitating neuropathic symptoms—mainly pain and dysautonomia—and occurs in up to 60% of sarcoidosis patients.<sup>93</sup> Often under-recognized, diagnosis requires large fiber disease exclusion and is facilitated by skin biopsy and sudomotor testing.<sup>94</sup> Since there is no established treatment, palliative treatment on a case-by-case basis may include tramadol, anticonvulsants, topiramate, gamma-aminobutyric acid analogues, and intravenous immunoglobulin.<sup>95</sup>

### CONCLUSION

Treatment of a patient with sarcoidosis should take into account not only physiologic impairment of the organ but also quality of life and patient-reported outcomes. Corticosteroids, the first-line treatment for acute and chronic disease, should be employed at the lowest affordable dose. To allow this, steroid-sparing agents, in particular methotrexate, are useful and effective. Infliximab, among anti-TNF agents, is effective in refractory pulmonary,

cutaneous, and neurosarcoidosis. Patients with advanced disease, pulmonary fibrosis, pulmonary hypertension, cardiac sarcoidosis, and neurosarcoidosis should be thoroughly identified and treated accordingly. Fatigue and small fiber neuropathy impose significant burdens to patients, and efforts should be made to relieve them.

### KEY POINTS

- Treatment goals in sarcoidosis are preventing permanent end-organ dysfunction and preserving quality of life.
- Corticosteroids remain the first-line treatment, although with significant cumulative side effects.
- Second- and third-line agents may be used in refractory or relapsing disease or when corticosteroids cause unacceptable toxicity; methotrexate and infliximab have shown important efficacy with acceptable safety profile in cardiac sarcoidosis.
- Advanced sarcoidosis refers to high mortality disease manifestations (pulmonary fibrosis, pulmonary hypertension, cardiac sarcoidosis, and neurosarcoidosis) and necessitates treatment.
- Cardiac sarcoidosis requires immunosuppressive treatment and recognition of patients at risk for sustained arrhythmias, which have to be managed thoroughly.
- Long-term maintenance therapy remains controversial.

## COMPETING INTERESTS

The authors have no competing interests to declare.

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TO CITE THIS ARTICLE:

Papanikolaou IC, Antonakis E, Pandi A. State-of-the-Art Treatments for Sarcoidosis. *Methodist DeBakey Cardiovasc J*. 2022;18(2):94-105.  
doi: 10.14797/mdcvj.1068

Submitted: 19 November 2021 Accepted: 01 February 2022 Published: 14 March 2022

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