# Pulmonology meets rheumatology in sarcoidosis: a review on the therapeutic approach

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**Purpose of review**
Sarcoidosis is a systemic disease characterized by the formation of granulomas in various organs, mainly lungs and lymphatic system. Joint, muscle, and bone involvement is also rather common. Recent studies on its pathogenesis and therapeutic management are reviewed here.

**Recent findings**
The pathogenesis of sarcoidosis is not fully elucidated. An exaggerated granulomatous reaction after exposure to unidentified antigens in genetically susceptible individuals evokes a clinical situation which we call sarcoidosis. No firm guidelines exist on whether, when, and how treatment should be started. Treatment is dependent on the presentation and the distribution, extensiveness and severity of sarcoidosis. Treatment of Löfgren's triad-related symptoms starts with NSAIDs; in other more extensive manifestations of sarcoidosis, the initiating dosage of glucocorticosteroids is approximately 20 mg daily. In terms of evidence-based treatment for sarcoidosis, only a few randomized controlled trials have been done. There is no cure for chronic sarcoidosis, and treatment only changes the granulomatous process and its clinical consequences.

**Summary**
Identified associations of certain polymorphisms with severity of the disease and treatment response suggest future research questions as well as finding the cause(s) of sarcoidosis, and the elucidation of relevant biomarkers and new efficient treatments. Between 20 and 70% of patients need systemic therapy. The increased awareness of long-term side-effects of glucocorticosteroids and the emergence of new drugs have changed the treatment of sarcoidosis. Alternative or additional options to corticosteroids should be assessed.

**Video abstract**
http://links.lww.com/COR/A13

**Keywords**
arthritis, Löfgren's syndrome, rheumatic diseases, sarcoidosis, sarcoidosis treatment

## INTRODUCTION

Sarcoidosis is a systemic often multiorgan disease of unknown cause, characterized by inflammatory activity with formation of noncaseating granulomas in various organ systems [1,2▪▪]. The presentation and course of sarcoidosis are highly variable, depending on the individual's ethnicity, the specific site and extent of organ involvement, and the fluctuating activity of the granulomatous process [1]. It primarily affects the lungs, but patients may develop involvement of virtually any organ system, including locomotor complications [1,2▪▪,3]. Patients can present with various clinical signs and symptoms depending on the organs involved as well as extent of the disease [1,3–5]. Appreciation of unexplained persistent disabling symptoms, such as pain, fatigue, small-fiber neuropathy (SFN), and cognitive failure has improved. These symptoms can be disabling and have a substantial impact on the quality of life of patients and their families [1,2▪▪,4,6,7].

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## KEY POINTS

- Sarcoidosis is a complex multiorgan disease in which, apart form organ-related symptoms, nonspecific symptoms such as pain, fatigue, exercise intolerance, and muscle weakness are common, making a multidisciplinary approach mandatory.
- Sarcoidosis patients may present with any number of rheumatologic symptoms; these manifestations often have an acute presentation, such as Löfgren's triad, or follow a more chronic disease course; both necessitate different therapeutic approaches.
- The therapeutic approach of Löfgren's triad consists of clear communication to the patient, and a wait-and-see policy with predominant symptom relief using NSAIDs; in other more extensive manifestations of sarcoidosis, the initiating dosage of glucocorticosteroids is approximately 20 mg daily.
- Second-line treatment consists of one or more DMASDs with or without glucocorticosteroids, with MTX being the preferred cornerstone of second-line agents; third-line options consist of anti-TNF-α agents or experimental therapeutics such as rituximab.

## CAUSE

Although there has been tremendous progress in understanding the pathogenesis, the cause of sarcoidosis remains unclear [2▪▪]. Sarcoidosis is probably the end result of a process consisting of an immune response to a variety of environmental triggers in a genetically susceptible individual, in which also oxidative stress appears to play an important role [5].

The development and accumulation of non-caseating granulomas constitute the fundamental abnormality in sarcoidosis [1,2▪▪]. Granulomatous inflammation is mediated by an antigen-induced, antigen-specific, Th1-mediated response with production of Th1 cytokines [interferon (IFN)-γ, interleukin (IL)-2]. Granuloma formation is set in motion by activated macrophages and T cells along with other effector cells, such as tumor necrosis factor-alpha (TNF-α), with amplification of the local cellular immune response. Removal of the antigen allows down-regulation of the immune hyperresponse. Macrophages activated in the context of a predominant Th2 response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis [2▪▪].

Sarcoidosis probably requires exposure to one or more exogenous agents (given below) [2▪▪,8].

(1) Infectious exposures
   (a) Mycobacterium
   (b) Propionibacterium acnes
   (c) Herpes viruses
   (d) Microbial bioaerosols
(2) Noninfectious environmental and occupational exposures
   (a) Mold/mildew
   (b) Silicates
   (c) Inorganic dust
   (d) Musty odors
   (e) Pesticides/insecticides
   (f) Metalworking fluid aerosols
   (g) Wood stoves
   (h) Man-made mineral fibers
   (i) Talc and chalk

Familial clustering of sarcoidosis has also been demonstrated [2▪▪]. Genetic predisposition appears not to be dependent upon a single gene and/or polymorphism. Previous genetic studies have established a role for variants in the human leukocyte antigen (HLA) genes [1]. For example, carriage of HLA-DRB1*1101 and HLA-DPB1*0101 alleles is found to be a risk factor for chronic sarcoidosis, whereas HLA-DQB1*0201 and HLA-DRB1*03 are strongly associated with acute disease and a good prognosis [2▪▪,9,10]. An association has been found between the presence of a *TNF-α*-308A variant allele with a favorable prognosis [10].

An important role for oxidative stress in the cause of sarcoidosis has been proposed, as the consequence of an imbalance between the presence of and the protection against reactive oxygen species (ROS) [11,12]. ROS are capable of reducing endogenous defence levels and enhancing inflammation [11].

## RHEUMATOLOGIC MANIFESTATIONS OF SARCOIDOSIS

Rheumatologic manifestations of sarcoidosis include peripheral (peri)arthritis, sacroiliitis (arthritis of the sacroiliac joints), which may cause inflammatory lower back pain, with pain extending from the lower back to the buttocks, and osseous lesions. To date, myopathy occurs more frequently than osseous involvement, affecting up to 75% of all individuals with sarcoidosis. Similarly to bone involvement, myopathy is associated with chronic disease and a worse prognosis. Systemic vasculitis associated with sarcoidosis is uncommon [3].

A frequently occurring acute rheumatologic presentation of sarcoidosis is Löfgren's triad, which is characterized by bilateral ankle periarthritis (one in three is also suffering from ankle arthritis), erythema nodosum, and bilateral hilar lymphadenopathy [1]. In some cases, patients may present with Lofgren's PLUS, consisting of the Löfgren's triad and

an additional abnormality, such as carpitis. These PLUS presentations have usually a more prolonged course.

As the differential diagnosis of arthritis is wide, it is important to consider exclusion of other causes. Arthritis can be due to crystals [13]. In severe cases, one should be particularly cautious. To differentiate bacterial from mono sodium urate crystal or pyrophosphate crystal arthritis, a joint puncture and polarization microscopy of the punctate need to be performed [13]. Only sporadically, these crystals co-present with sarcoidosis, possibly particularly in patients with a high urate production due to cellular degradation [13]. In cases without the demonstration of crystals in joint punctate, psoriatic or sarcoid arthritis has to be considered.

Bone and bone marrow lesions can be found in more than one-third of patients, as assessed by fluorine18-fluorodeoxyglucose-positron emission tomography ($^{18}$F-FDG PET) in a recent study [14▪]. This incidence was much higher than expected according to previously published data [2▪▪,3,14▪]. Previous data also suggest that sarcoidosis most commonly affects the phalanges of the hand and feet [3]. However, this finding was not supported by PET findings [14▪]. Sarcoidal osseous involvement has been associated with cutaneous lesions, such as lupus pernio and a chronic progressive disease course [2▪▪,3,14▪].

Rheumatologic manifestations may consist of pain and fatigue. Musculoskeletal pain in sarcoidosis can be the consequence of inflammatory articular or tenosynovial involvement, myopathy or bone lesions. However, SFN is another frequently occurring disabling problem in sarcoidosis, which can cause comparable symptoms (given below) [15]. Furthermore, SFN signs can mimic enthesopathy, resembling fibromyalgia symptoms. It is also associated with other autoimmune diseases.

Symptoms suggestive of SFN, adapted from Hoitsma *et al.* [15]:

(1) Sensory symptoms
   (a) Pain (burning, tingling, shooting, prickling in character)
   (b) Paraesthesias
   (c) Sheet intolerance
   (d) Restless legs syndrome, periodic leg movements
(2) Symptoms of autonomic dysfunction
   (a) Hypohidrosis or hyperhidrosis
   (b) Diarrhea or constipation
   (c) Urinary incontinence or retention
   (d) Gastroparesis
   (e) Sicca syndrome
   (f) Blurry vision
   (g) Facial flushes
   (h) Orthostatic intolerance
   (i) Sexual dysfunction

## THERAPEUTIC OPTIONS

The published data on the different treatment options in sarcoidosis are limited [16▪,17,18▪]. The decision to treat either immediately or during follow-up is guided by three factors: risk of severe dysfunction or irreversible damage to major organs, risk of death, or the presence of incapacitating, constitutional symptoms. The main indications for treatment are apart from respiratory functional impairment, involvement of the cardiac, neurological, or renal systems; ocular sarcoidosis that does not respond to topical therapy; and symptomatic hypercalcemia. Treatment is dependent on the sarcoidosis presentation and the distribution, extensiveness and severity of other sarcoidosis organ involvement. Most sarcoidosis patients show spontaneous resolution of the disease and do not require systemic therapy [16▪]. However, for patients with a severe disease course and poor prognosis, a timely implementation of a potent individual treatment regimen is important to avoid or slow down the development of complications and to alleviate the disease burden.

The presence of acute and fulminant Löfgren's triad is associated with a good prognosis with usually spontaneous resolution within 1–2 years [1,2▪▪,16▪]. In general, a wait-and-see policy with symptom relief using NSAIDs, if necessary, is the correct therapeutic approach. Sometimes a severe periarthritis of ankle may result in hyperextension of foot if untreated but just given bed rest. These severe cases may be prevented by adequate treatment with NSAID and walking. Nevertheless, since approximately 10% of these severe Löfgren patients do need long-term systemic therapy, a regular follow-up is advisable [16▪,19]. Patients with adverse prognostic factors, among which is extrapulmonary osseous involvement, are more likely to become chronic, requiring long-term pharmacotherapeutic treatment [1,16▪,20]. The presence of chronic sarcoid arthritis may also warrant long-term systemic therapy.

### First-line therapy: NSAIDs and glucocorticosteroids

Several pharmacological options exist for sarcoidosis patients who require therapy. However, none of these drugs is curative, but they are more bridging a fulminant phase. In sarcoid arthritis, NSAIDs can be effective for symptom relief [3,18▪]. Glucocorticosteroids are considered the first-line therapy for

**Table 1.** Summary of drugs used in the treatment of sarcoidosis organised by manifestation with level of evidence

| Drug | Indication | Level of evidence[a] |
|---|---|---|
| NSAIDs | Löfgren's triad, pain | NA |
| Glucocorticosteroids* | | |
| Prednison | Sarcoidosis activity in general | 1A |
| Cytotoxic drugs* | | |
| Methotrexate (MTX) | Refractory sarcoidosis | 1B |
| Azathioprine (AZA) | Cardiac involvement, neurosarcoidosis, uveitis, skin lesions, arthritis, refractory skin lesions | 2B |
| Leflunomide (LEF) | | 2B |
| Cyclophosphamide | | 4 |
| Mycophenolate mofetil (MMF) | | 4 |
| Antimicrobial drugs | Skin lesions, lupus pernio | |
| (Hydroxy)chloroquine ((H)CQ) | | 2B |
| Cytokine modulators | | |
| Pentoxifylline (POF) | Pulmonary involvement, skin lesions | 2B |
| Thalidomide | | 4 |
| Apremilast | Skin lesions, lupus pernio | 4 |
| Anti-tumor necrosis factor-alpha (TNF-α) agents | Skin lesions | |
| Infliximab | Refractory severe sarcoidosis not responding to glucocorticosterods or cytotoxic drugs | 1B |
| Adalimumab | | 2B |
| New experimental treatment modalities | | |
| Rituximab (RTX) | In refractory severe cases who failed to respond to the drugs mentioned above | 4 |
| Quercetine | Supportive treatment | 1B |
| D-methylphenidate (D-MPH) or methylphenidate | Fatigue | 1B |
| Immunoglobulins | Small fiber neuropathy, fatigue and pain | 4 |
| ARA 290 | Small fiber neuropathy, fatigue and pain | 1B |

[a]Level of evidence, according to the Oxford Centre for Evidence-Based Medicine.
NA, not applicable.
*Note: Less useful in case of small fiber neuropathy.

chronic pulmonary and extrapulmonary sarcoidosis [17,18▪,19]. Their use in sarcoid arthritis has been shown in case reports [3]. Generally, prednisone dosages of 20 mg daily are sufficient for sarcoid arthritis disease management. Higher dosages have not been proven to be more effective, whereas they can be accompanied with a higher risk of significant side-effects, such as weight gain/obesity, diabetes mellitus, cataract or osteoporosis [2▪▪]. Adjustments to treatments should be made according to clinical presentation. Patients with chronic sarcoidosis might need low-dose treatment for many years, whereas treatment for 3–6 months might be adequate for patients with acute forms of disease. Although systemic corticosteroid treatment for symptomatic sarcoidosis has short-term benefits, there is little evidence for long-term effect [2▪▪]. Therefore, glucocorticosteroids are undesirable for chronic disease management [2▪▪,18▪]. Tapering to the lowest effective dose is an ultimate treatment goal and alternative glucocorticosteroid-sparing treatment agents are to be considered [2▪▪,5,16▪,17,18▪]. In steroid-refractory cases, second-line drugs, which are referred to as disease-modifying antisarcoid drugs (DMASDs), and third-line therapies, offer alternative strategies [5,16▪,17,18▪]. The increased awareness of long-term side-effects of glucocorticosteroids and the emergence of new drugs have changed the treatment of sarcoidosis. Alternative or additional options to corticosteroids should be assessed (see also Table 1). In general, but especially in sarcoidosis patients with suspected corticosteroid-induced osteoporosis, it is sensible to measure serum and urinary calcium and serum 1,25(OH)2 vitamin D3 concentrations [21,22]. Bisphosphonate treatment should be chosen as the initial strategy for primary prevention of corticosteroid-induced osteoporosis [21]. Appropriate vitamin D and calcium supplementation in sarcoidosis remains controversial [22]. It is suggested that a low serum 1,25(OH)2 vitamin D3 should be

treated [21]. However, in case of hypercalciuria with or without signs of systemic hypercalcemia, caution is warranted. Systemic hypercalcemia necessitates treatment [22].

## Second-line therapy: disease-modifying antisarcoid drugs

Several agents have been used as DMASDs in both pulmonary and extrapulmonary sarcoidosis (Table 1) [2▪▪,3,4,5,11,17,18▪,23,24▪,25–41].

### Methotrexate

Next to glucocorticosteroids, methotrexate (MTX) has been the most widely studied therapeutic agent for sarcoidosis [17,42▪▪]. It is considered the first-choice DMASD used for patients with sarcoidosis, with 80% of physicians reporting MTX as their preferred second-line option [16▪]. MTX is useful as a steroid-sparing agent, as has been shown by the single available high-quality randomized controlled trial ($n = 24$) [23]. A recent retrospective cohort study [24▪], comparing the DMASDs MTX and azathioprine (AZA) in sarcoidosis ($n = 200$), showed a significant steroid-sparing potency and a positive effect on lung function of MTX. Large case series have also shown the use of MTX in pulmonary and extrapulmonary sarcoidosis [42▪▪,43]. The effectiveness of MTX in musculoskeletal and joint sarcoidosis involvement has been shown in case reports [3,24▪]. Recently, international recommendations for the use of MTX in sarcoidosis have been established [42▪▪]. A starting dosage of MTX of 5–15 mg weekly is recommended, either perorally or subcutaneously [42▪▪]. Administration of folic acid reduces gastrointestinal and hepatic toxicity with only a modest negative effect on efficacy [42▪▪,44].

### Azathioprine

Azathioprine (AZA) has been reported as effective in treating pulmonary and extrapulmonary sarcoidosis [17]. The reports usually have been case series. Compared to MTX, AZA demonstrated a similar efficacy in pulmonary and extrapulmonary sarcoidosis [18▪,24▪]. Both drugs were shown to be effective steroid-sparing agents in pulmonary sarcoidosis. AZA is metabolized by the enzyme thiopurine S-methyltransferase (TPMT) to 6-mercaptopurine [17]. It is associated with nausea and leucocytopenia [17]. Furthermore, it can lead to severe hepatotoxicity [17]. Patients with low or deficient TPMT levels are at higher risk of developing drug-related toxicity [45]. Therefore, measuring TPMT before initiating AZA therapy is recommended [45].

### Leflunomide

Leflunomide (LEF) is primarily used as an alternative or if needed in addition to MTX [17,18▪]. However, there are no studies directly comparing the effectiveness and side-effects of LEF and MTX. A complete or partial response for cutaneous, ocular, and sinonasal involvement was seen, but LEF was less effective for neurological and musculoskeletal manifestations [18▪]. Major toxicities are similar to MTX [17,18▪].

### Chloroquine and hydroxychloroquine

The antimalarial agents chloroquine and hydroxychloroquine (HCQ) are both effective for cutaneous sarcoidosis [17,18▪]. Especially chloroquine is associated with significant ocular toxicity, which is dose-dependent [17].

### Other less commonly used second-line options

A recent study found significantly reduced daily glucocorticosteroid doses in patients with chronic pulmonary sarcoidosis treated with mycophenolate mofetil (MMF) [18▪,26]. MMF might have a role in neurosarcoidosis affecting the central nervous system [46].

Treatment with pentoxifylline (POF) achieved improvement of diffusing capacity for carbon monoxide in acute pulmonary sarcoidosis [2▪▪]. However, due to gastrointestinal toxicity its use in chronic sarcoidosis is limited [17,20].

Thalidomide appeared to be effective and steroid-sparing in the treatment of chronic cutaneous as well as pulmonary sarcoidosis by inhibition of TNF-α production [2▪▪]. Side-effects include peripheral neuropathy, hypersomnolance, and an increased risk for deep venous thrombosis and pulmonary embolism [2▪▪].

## Third-line therapy: anti-TNF-α agents and new experimental treatment modalities

For some patients with sarcoidosis, glucocorticosteroids and (combinations of) DMASDs may not control disease [17]. Several biological agents which specifically inhibit TNF-α have demonstrated efficacy in sarcoidosis, especially in patients refractory to other treatments [17,18▪]. Furthermore, some new experimental treatment modalities can form alternative third-line therapeutic options [17,18▪].

### Anti-TNF-α agents

Tumor necrosis factor-alpha inhibitors might be a valuable treatment option for patients with pulmonary and/or extrapulmonary sarcoidosis refractory to conventional therapy, on the condition that

they are used with caution [18▪]. Infliximab is a biological chimeric monoclonal antibody that binds to free TNF-α, blocking its interaction with the TNF-receptor, and sometimes to cell surface TNF-α [2▪▪]. Two double-blind, placebo-controlled trials of infliximab in patients with chronic pulmonary sarcoidosis showed a significant improvement of forced vital capacity [28,29] and in one study [28] improvement in chest radiographs. Judson *et al.* [47] used an extrapulmonary physician organ severity tool for evaluation of specific organ involvement in sarcoidosis. Although the sample size was low, their results suggest that infliximab may be beneficial in extrapulmonary sarcoidosis. A recent retrospective study [27] investigated the sustainability of infliximab response in pulmonary and extrapulmonary sarcoidosis for up to 85 months and concluded that infliximab has the capacity to maintain improvements in sarcoidosis over time, based on the finding that 59% of the organs evaluated achieved improvement. Single instances of bone and muscle sarcoidosis demonstrated resolution of disease with infliximab therapy [27]. In contrast to treatment of rheumatoid arthritis (RA), the dosage needed in sarcoidosis is often 5 mg/kg per week every 4 weeks.

Adalimumab is a recombinant fully human monoclonal antibody against TNF-α [17]. Prospective observational studies have shown effectiveness of adalimumab in treating refractory posterior uveitis [30], in decreasing total sarcoidosis disease activity as measured by PET [31], and in improving radiological abnormalities [2▪▪]. Adalimumab also has a positive effect on cognition and fatigue in sarcoidosis [36]. Furthermore, a recent study [37] has shown adalimumab to be a possible effective and relatively well tolerated treatment in cutaneous sarcoidosis. When starting adalimumab, the loading dosage is 80–120 mg in the first week and thereafter 40–80 mg weekly dependent on the extent of sarcoidosis.

Etanercept is a TNF-receptor antagonist [17]. Etanercept is not used in sarcoidosis disease management. In an open-label trial of pulmonary sarcoidosis, etanercept alone was associated with treatment failure in 12 of 17 cases [48]. Furthermore, the drug failed in a double-blind, placebo-controlled trial of patients with refractory sarcoidosis uveitis [17].

Wijnen *et al.* [49▪] showed a response rate of 75% for infliximab and adalimumab in refractory sarcoidosis. A possible role for pharmacogenetics by genotyping for the *TNF-α* G-308A polymorphism in order to predict TNF-α inhibitor response was demonstrated, illustrating a first step towards personalized medicine in sarcoidosis disease management. A difficult issue clinicians are struggling with is in which sarcoidosis patients and after what treatment duration maintenance of clinical remission is likely when tapering off TNF-α inhibitors. Vorselaars *et al.* [50] showed that the majority of sarcoidosis patients (29 of 47 patients, 62%) relapsed after discontinuation of infliximab after a mean treatment duration of 8.5 months. These results suggest that successful discontinuation only is probable after stable disease has been achieved.

For all anti-TNF-α agents, similar toxicities or side-effects have been reported [51]. The concurrent use of MTX or other cytotoxic drugs has been advised to reduce the risk of antibody formation in RA, but also in sarcoidosis [52]. A recent study [53] in RA shows that adalimumab levels are influenced by concomitant MTX use: patients on adalimumab monotherapy had a median adalimumab level of 4.1 μg/ml [interquartile range (IQR) 1.3–7.7], whereas patients concomitantly taking MTX had a median level of 7.4 μg/ml (IQR 5.3–10.6, $P < 0.001$), with a better clinical response for patients using both adalimumab and MTX. A likely explanation is that patients with concomitant MTX are less prone to antibody formation. There is a marked increased risk for reactivation of tuberculosis and increased severity of tuberculosis course associated with the use of anti-TNF-α agents [18▪]. Prior to starting anti-TNF-α therapy, screening for latent tuberculosis, using interferon-gamma release assays (IGRAs), is recommended [17,18▪,54]. Furthermore, there have been several reports of sarcoidosis-like reactions during the use of anti-TNF-α agents in other diseases. Fortunately, the prognosis is good, with complete resolution of the event after discontinuation in most cases [17,18▪,55].

## New experimental treatment modalities

Rituximab (RTX), a chimeric monoclonal antibody that targets CD-20 cells, reduces the number of mature B lymphocytes in the circulation after several months [17,18▪]. It has been reported as effective for refractory sarcoidosis in case reports [32–34,38]. The drug has some toxicity, including B lymphocytopenia, neutropenia and hypogammaglobulinemia, and increased risk for viral infections [17,34].

The antioxidant quercetin has shown to have beneficial effects in sarcoidosis [11]. This flavonoid offers protection against ROS-induced oxidative damage and has anti-inflammatory capacities by a reducing effect among other TNF-α [11].

A new phosphodiesterase inhibitor, apremilast, has been reported as effective for chronic cutaneous sarcoidosis [17,18▪,35].

Abatacept and tocilizumab have been successfully used in RA [56,57]. Regarding their immunopharmacological mode of action, one might

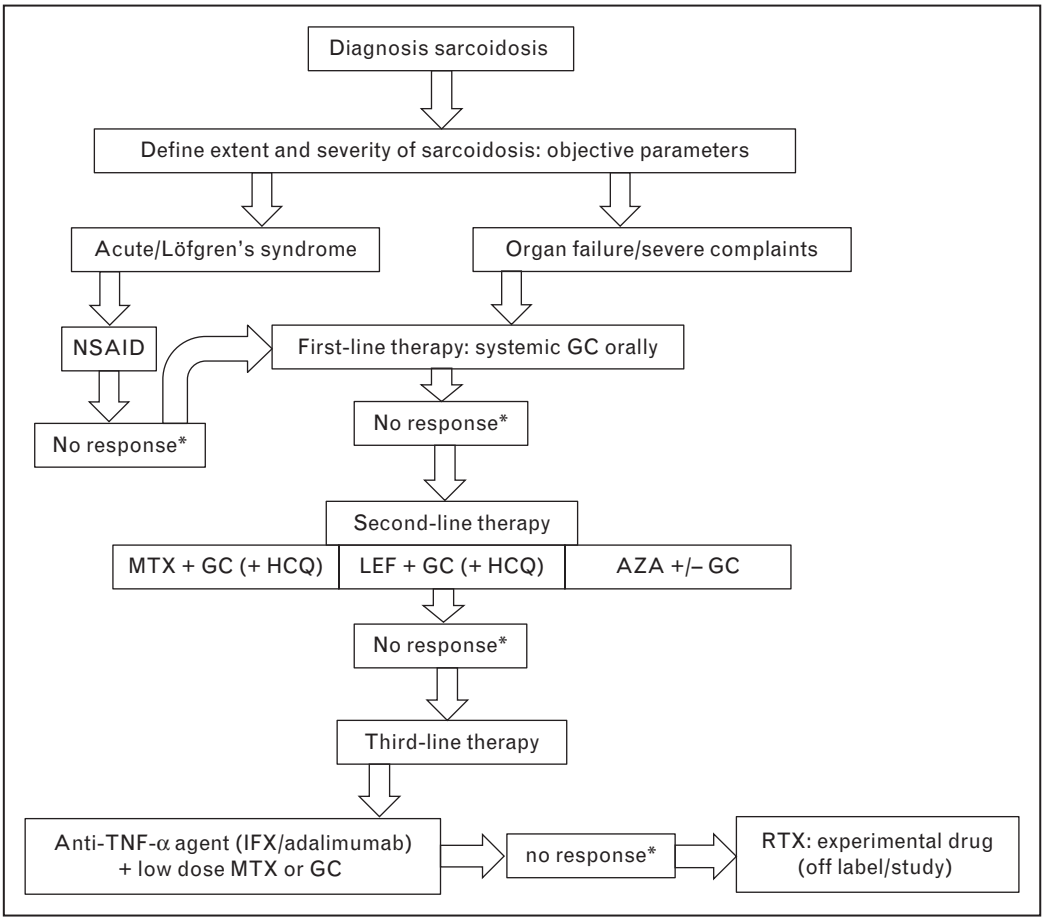


**FIGURE 1.** Therapeutic approach of patients with sarcoidosis, including rheumatic manifestations. (*) In case of inadequate response, progressive disease or drug intolerance. AZA, azathioprine; GC, glucocorticosteroids; HCQ, hydroxychloroquine; IFX, infliximab; LEF, leflunomide; MTX, methotrexate; p.o., per orally; RTX, rituximab; TNF-α, tumor necrosis factor-alpha.

consider them as promising in sarcoidosis as well. Data are lacking though.

Since SFN needs a specified treatment approach, it is important to be aware. In general, SFN features do not respond to the standard anti-inflammatory treatment options for sarcoidosis or to regular neuropathic pain therapeutics, such as antidepressant, anticonvulsants, topical anesthetics, and opioids [15,18▪,40,58]. Intravenous immunoglobulins seem to be promising, but require further study [15,18▪,40,58]. A novel therapy is ARA 290, a non-hematopoietic erythropoietin analog designed to activate the innate repair receptor, with potent anti-inflammatory and tissue-protective properties [15,41]. Recently, the efficacy of ARA 290 was shown in a pilot study [41] in patients with sarcoidosis suffering from SFN.

## APPROACH FOR MANAGEMENT OF SARCOIDOSIS

The therapeutic approach of rheumatic manifestations of sarcoidosis does not differ from the treatment of sarcoidosis in general. After establishing the diagnosis and defining the extensiveness and severity of sarcoidosis, including joint, muscle, bone and other organ involvement, the proposed approach for the management of sarcoidosis is shown in Fig. 1. The therapeutic approach of a fulminant Löfgren's triad consists of a wait-and-see policy with primarily symptom relief using NSAIDs. In other presentations, a more active, systemic pharmacotherapeutic approach consisting of oral prednisone may be needed. In general, prednisone dosages of approximately 20 mg daily are sufficient for adequate disease management depending on the disease presentation, organs involved and extent of the disease. In non-responders, with inadequate response or progressive disease, or in case of glucocorticosteroid-associated side-effects, this regime can be combined with the second-line therapeutic MTX if patients are MTX-naïve or have been previously successfully treated. MTX can be combined with HCQ. In cases of intolerance, AZA or LEF. . .etc may be considered instead of MTX. In refractory sarcoidosis, combination therapy

consisting of low doses of prednisone or MTX in combination with an anti-TNF-α agent (infliximab or adalimumab) may be needed. In case of primary response with secondary ineffectiveness, insufficient efficacy after 6 months of this third-line combination therapy should lead to consideration of switching to another anti-TNF-α agent. In case of primary ineffectiveness, off-label use of rituximab can be considered. For nonspecific, disabling symptoms such as exercise intolerance, muscle weakness, fatigue and pain, physical testing can offer added value in the screening and follow-up [6,59]. Since exercise training has proved effective in several chronic diseases, its value in sarcoidosis management is likely to be beneficial.

## CONCLUSION

The clinical course for sarcoidosis varies. No firm guidelines exist on whether, when, and how treatment should be started. The choice of treatment should be guided not only by the rheumatologic sarcoidosis manifestations, but also on the distribution, extensiveness and severity of general manifestations. The decision to treat either immediately or during follow-up is guided by three broad factors: risk of severe dysfunction or irreversible damage to major organs, risk of death, and/or the presence of incapacitating, constitutional symptoms. The main indications for treatment are involvement of the cardiac, neurological, or renal systems; ocular sarcoidosis that does not respond to topical therapy; and symptomatic hypercalcemia. First-line treatment options consist of NSAIDs and glucocorticosteroids. Second-line treatment consists of one or more DMASDs with or without glucocorticosteroids, with MTX being the preferred second-line agent. Third-line options consist of anti-TNF-α agents or experimental therapeutics such as RTX.

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### Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- ■■ of outstanding interest

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