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Treatment of Sarcoidosis

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Abstract In general, sarcoidosis treatment should be offered to palliate symptoms and improve quality of life or to prevent end-organ disease. Symptoms include pulmonary as well as extra-pulmonary manifestations of the disease. The assessment of response to disease includes functional studies such as the forced vital capacity. Radiologic imaging such as chest x-ray has also been used to assess response, although standardized measures have rarely been tested. There are sufficient clinical trials to make specific recommendations regarding treatment of symptomatic pulmonary disease. Initial therapy is usually prednisone or a similar glucocorticoid. However, there are several features of this treatment which are unknown. This includes the initial dose, timing of reduction of dose, and when to discontinue treatment. Since many patients are intolerant of prednisone, steroid-sparing alternatives have been studied. Methotrexate is the most widely used anti-metabolite, but azathioprine, leflunomide, and mycophenolate have also been reported as helpful. The biologic agents, especially monoclonal anti-tumor necrosis factor (anti-TNF) antibodies, have proved effective in patients who have failed other treatments. Infliximab, the most widely studied anti-TNF antibody, has proved effective for a range of refractory sarcoidosis. However, there remain questions regarding dose and duration of therapy. For the clinician, the many treatment options allow for a specific treatment regimen for each patient which minimizes risk while enhancing benefit.

Keywords Prednisone · Infliximab · Pulmonary sarcoidosis · Methotrexate

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Introduction

In general, sarcoidosis treatment should be offered to palliate symptoms and improve quality of life or to prevent end-organ disease. The treatment of sarcoidosis remains a mixture of evidence-based recommendations and clinical judgment. Although there are an increasing number of potential pharmacologic treatment strategies, the potential benefit and therapeutic indications for individual drugs remains unclear. In most patients, a step-wise approach is employed. For some patients, no systemic therapy is indicated. In those in whom systemic treatment is employed, glucocorticoids remain the first choice. Unfortunately, many patients will require therapy for years. In these patients, long-term treatment with glucocorticoids could lead to significant morbidity. In these situations, alternatives to glucocorticoids may prove useful. There have been several steroid-sparing alternatives which have been investigated. These include the anti-metabolites methotrexate, azathioprine, leflunomide, and mycophenolate and the biologic agents infliximab and rituximab. In this review, we will examine the indications for treatment and assess treatment response for pulmonary and extra-pulmonary manifestations. In addition, we will discuss the various medications and their role in treating these conditions.

Indications for Therapy

Pulmonary Disease In most reported series of the disease [1–3], lung involvement occurs in over 90 % of sarcoidosis patients. However, only half of these patients will require

systemic therapy [3]. Lung involvement can lead to symptoms including dyspnea, cough, and chest pain. Dyspnea, the most common pulmonary complaint [4], is related to the degree of lung involvement as assessed by either chest x-ray [4] or pulmonary function. However, over a third of patients with grade 4 dyspnea, the most severe on medical research council (MRC) score, had normal forced vital capacity (FVC) (Fig. 1). This disconnect between traditional chest x-ray, FVC, and level of dyspnea points out that we may be underestimating lung involvement. Also, dyspnea in sarcoidosis can be due to multiple factors (Table 1). In evaluating a dyspneic sarcoidosis patient, the clinician should be aware that one or more factors may be the cause of dyspnea. Consequently, treatment directed against any one factor may not relieve dyspnea.

Direct pulmonary disease can be due to interstitial lung disease. Evaluation for interstitial lung disease includes not only spirometry and DLCO but also chest imaging. These tests are complimentary and provide a level of confirmation [6].

The most commonly used test to assess response to therapy is the FVC [6, 7]. A generally agreed upon treatment target is greater than 10 % improvement in FVC percent predicted [6]. In open-label trials, the FVC has been reported to improve by more than 10 % in a significant number of patients treated with various agents, including prednisone [8], methotrexate [9, 10], azathioprine [9], and infliximab [11, 12]. However, studies comparing treatment versus placebo have usually failed to demonstrate such a robust response to treatment. Figure 2, which summarizes the response seen in these studies, confirms that the response was less than 10 % in all studies.

Additional pulmonary function testing includes the diffusion in lung of carbon monoxide (DLCO) and exercise testing. The DLCO appears more sensitive to changes in pulmonary parenchymal disease. For sarcoidosis patients with pulmonary disease, a higher proportion will demonstrate changes in the DLCO abnormalities and lower values than the FVC [18]. However, the DLCO is less likely to change with therapy [19]. Additionally, the DLCO may be of limited value because a lower DLCO may be caused by other problems unrelated to parenchymal lung disease such as pulmonary hypertension, anemia, and co-existing bullous lung disease.

The modest functional improvement seen with infliximab highlights the damping effect of baseline therapy on response to new treatment. In the two placebo-controlled trials, patients were on stable treatment received either infliximab or placebo [16, 17]. Most patients were receiving significant doses of prednisone at study initiation. In a post hoc analysis of one of these studies [16], Judson et al. found that the response to infliximab was associated with baseline dosage of prednisone [20]. Patients treated with more than 20 mg a day of prednisone or its equivalent were unlikely to have any response to infliximab therapy. This is not entirely surprising, since glucocorticoids suppress the release of tumor necrosis factor (TNF) from macrophages [21]. High-dose prednisone therapy may have totally blocked circulating TNF, the target of infliximab, a monoclonal antibody to TNF.

Given the limited improvement in FVC with treatment, other measures of treatment benefit have been proposed.

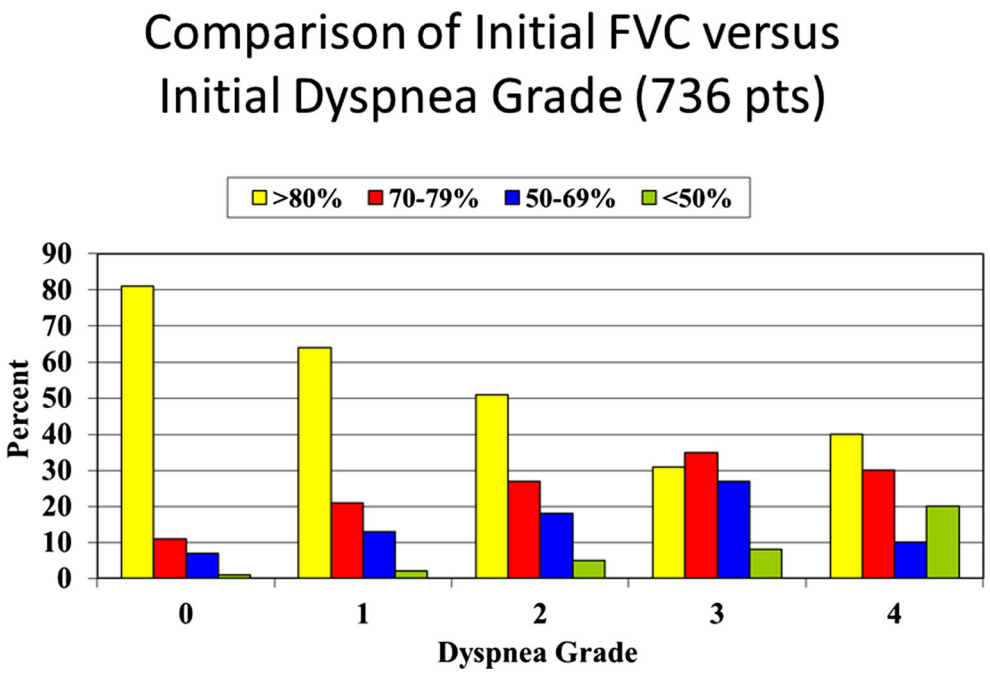

Fig. 1 Comparison of FVC percent predicted versus level of dyspnea. Dyspnea was scaled using the modified Medical Research Council score, with 0 being no dyspnea and 4 being the most severe [5]. Adapted from Baughman et al. [1]

Table 1 Causes of dyspnea in sarcoidosis

	Detection
Pulmonary involvement	
Interstitial lung disease	Spirometry, DLCO, chest imaging
Airway disease	Spirometry
Small airway	Spirometry
Large airways	Chest imaging
Upper airways	Chest imaging
Pulmonary vascular involvement	
Pre-capillary pulmonary hypertension	Echocardiography, right heart catheterization
Cardiac	
Arrythmias	Holter
Cardiomyopathy	Echocardiography
Myopathy/myositis	
Respiratory muscles	Inspiratory muscle pressure
Skeletal muscles	
Psychosocial	
Fatigue	Questionnaires
Depression	
Anemia	Complete blood count

Chest imaging can identify parenchymal lung disease, and the most commonly used test remains the chest x-ray. Scadding proposed a chest x-ray staging system which can reliably predict the outcome of a patient's chest x-ray over time [14]. Because of the reproducibility difficulties during treatment [22], the staging system is unreliable in assessing response to therapy. Muers et al. have developed a chest x-ray scoring system [23] which has proved useful in determining response to treatment with glucocorticoids [15] and infliximab [16, 22]. However, this technique is cumbersome and is limited to research studies. Blinded comparison x-ray studies before and after therapy have proved reliable in assessing response to treatment [22, 24, 25]. However, changes in chest x-ray are less frequent than changes in FVC. Because these tests appear complimentary, measurement of both of these tests seems appropriate in assessing response to treatment [6].

Other imaging techniques such as high-resolution computer tomography (HRCT) scan have proved useful detecting and characterizing the severity of manifestations especially fibrosis [26, 27]. However, no clinical trial to date has utilized changes in HRCT scan for assessing response. The lack of a standardized scoring system and consensus of which features on HRCT scan are important have proved problematic. Since the HRCT scan can simultaneously assess several features at the same time, one can monitor adenopathy, nodularity, and fibrosis equally well. However, it is not always clear which feature is the most important for an individual patient. Comparison between HRCT and pulmonary function testing have found correlations between various features of HRCT, such as fibrosis and DLCO while air trapping correlates with reduced forced expiratory volume in 1 s [28, 29].

PET scanning is potentially another method to assess response to treatment. Increased FDG uptake is a marker of inflammation [30]. The finding of baseline positive lung activity correlated with improvement with anti-inflammatory therapy. Conversely, positive lung activity in a patient not placed on systemic therapy was associated with worsening lung function [11, 31, 32]. In one large series, the original but not subsequent PET scan predicted the need for continued treatment with infliximab [33].

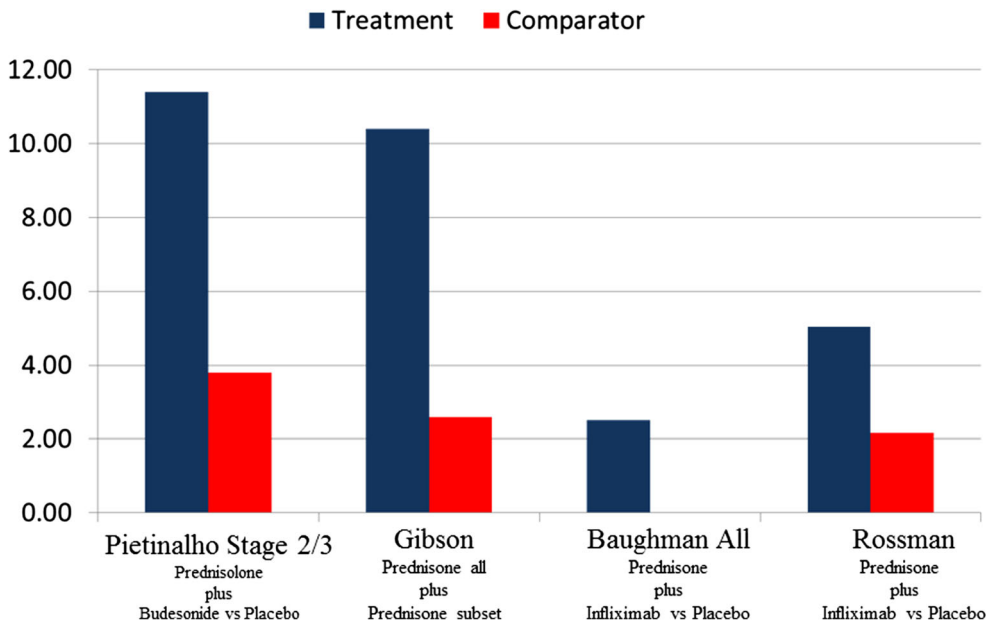

Fig. 2 Change in FVC% predicted (absolute change) between active drug versus placebo. For Pietinalho et al.'s [13] study, data is present for only those who presented with parenchymal infiltrates on chest x-ray (scadding stage 2 or 3 [14]). For Gibson et al.'s [15] study, over 10 % of patients initially not treated with prednisone received prolonged glucocorticoid therapy during the 18 months of the study. Patients in the studies by Baughman et al. [16] and Rossman et al. [17] received either infliximab or placebo in addition to stable immunosuppressive therapy

In summary, PET scanning is an expensive procedure and is associated with a relatively high radiation exposure. Therefore, its use in routine evaluation remains unclear. It may be most useful in identifying which patients would benefit from more expensive treatments such as infliximab [11, 30]. Relative PET activity in the lung parenchyma has been associated with severity of disease and response to treatment [31, 32]. A now rarely used nuclear imaging technique, quantitative gallium scan, has also been used to predict response to therapy [34].

Serum biomarkers have been proposed as means to monitor response to treatment. Early studies of angiotensin-converting enzyme (ACE) suggested that this enzyme could be used to monitor patients on corticosteroid therapy [35, 36]. However, subsequent studies found that ACE levels were independently suppressed by glucocorticoids [37, 38]. Serial ACE levels may still be useful to monitor in patients not treated with glucocorticoids [39]. The soluble interleukin-2 receptor (S-IL2r) has also been reported as a marker of chronic disease activity [40]. Because changes in S-IL2r may be less affected by corticosteroids, this biomarker may be a better reflection of disease activity [33].

Quality of life instruments have been used in clinical trials of sarcoidosis. These include the general pulmonary health Saint George Respiratory Questionnaire (SGRQ) and the overall health assessment short form 36 (SF-36) [41, 42]. However, the results of these tests were not specific. Also, a minimal clinically important difference for these questionnaires has not been determined in sarcoidosis as it has in other interstitial lung diseases [43, 44]. Recently, sarcoidosis-specific quality of life instruments have been developed [45, 46]. However, these have not been routinely applied to clinical trials. Future studies will probably include an interaction between functional studies and quality of life instruments [6].

There has been limited information regarding response assessment in extra-pulmonary sarcoidosis. For cutaneous sarcoidosis, several instruments have been reported [6]. These include the sarcoidosis activity and severity index (SASI) [47] and serial photographs [48]. Response assessment for ocular disease includes changes in visual acuity and a physician global assessment of inflammation [49].

The concept of glucocorticoid sparing can be a potential tool for evaluating patient response to treatment. Because many sarcoidosis patients are seeking alternatives to glucocorticoid therapy, the ability of a new drug to reduce the dosage of prednisone is often viewed positively. Some drugs such as methotrexate and azathioprine [50, 51] have been shown to be steroid sparing [50, 51]. However, few studies examined steroid withdrawal in a standardized fashion [52, 53].

Treatment of Sarcoidosis

Indications for treatment for pulmonary and extra-pulmonary disease are summarized in Table 2. Symptomatic disease is the major indication for treatment. In pulmonary disease, evidence exists that treatment of asymptomatic patients with parenchymal lung disease on chest x-ray (stage 2 or 3) will improve lung function compared to a placebo group [15, 54]. However, treatment with glucocosteroids for 18 months was associated with only a small response. In addition, most of the placebo-treated patients demonstrated stable to improved disease. Approximately 10 % of patients treated with placebo experienced clinical deterioration of their disease. These patients did respond to systemic therapy [15]. There is no evidence that long-term corticosteroids prevent fibrotic disease.

Table 2 Indications for systemic therapy

Pulmonary
Dyspnea
Cough
Ocular pain or loss of vision
Cosmetically disturbing skin lesions
Congestive heart failure
Cardiac arrhythmias
Neurologic impairment due to mass lesion or meningitis
Hypercalcemia
Nephrocalcinosis
End-organ failure

While cough is a common complaint in sarcoidosis, there is little evidence that any specific therapy will reduce this symptom. One study was able to determine that inhaled glucocorticoids therapy associated with a reduction in the frequency and severity of cough in patients compared to placebo-treated patients [53]. That study used a Likert scale for symptoms and did not validate the score versus objective measures such as cough counting. There have been no other placebo-controlled trials looking at cough.

Glucocorticoids and Glucocorticosteroid-Like Agents

Prednisone/Prednisolone While glucocorticoids have been shown to be better than placebo in improving lung function and chest x-ray in pulmonary sarcoidosis (Table 3) [68], there remain several unanswered questions (Table 4). The initial and subsequent dose of prednisone or similar agents is unclear. The treatment of sarcoidosis with glucocorticoids follows several stages, including initial treatment dose, tapering schedule, maintenance dose, duration of therapy, and dose for exacerbation [69]. The initial dose of prednisone varies considerably from study to study [8, 57, 70]. Most studies employ an initial dose ranging from 20 to 40 mg of prednisone daily or its equivalent. The duration of therapy also varies. In most

Table 3 Evidence to support use of glucocorticoid therapy for pulmonary sarcoidosis: improves lung function or chest x-ray in symptomatic disease

	DBPCRT	OLRT	Case series
Prednisone/prednisolone/methylprednisolone	Yes Israel [55] FVC, CXR James [56] CXR Selroos [57] FVC, DLCO, CXR	Yes Sharma [8] FVC Gibson [15] FVC, DLCO, CXR Spratling [58] FVC, DLCO, CXR No Harkleroad [59] FVC	Yes Johns [60] McKinzie [25] FVC
Inhaled steroids	Yes Alberts [61] FVC, CXR Pientello [13] FVC, DLCO No Milman [62] FVC Du Bois [63] FVC Baughman [53] FVC Zych [64] FVC	Yes Selroos [65] FVC, CXR	
Acthar			Yes Miller [66] Sones [67]

studies, treatment is for 6–18 months. This is in part because early studies demonstrated a high relapse rate if patients only received 3 months of therapy [70]. However, withdrawal of therapy after 6–18 months is still associated with a relapse rate that ranges from 30 to 80 % [71–74]. This has led to a suggested regimen of prolonged maintenance therapy, often for years. The dose of maintenance therapy is usually empiric, based on patient's own response. In one large study of sarcoidosis patients treated at one clinic in USA, many patients were maintained on an average of 10 mg of prednisone a day with some patients receiving as much as 20 mg a day or higher [60]. This approach has led to the proposal that there is a dose of glucocorticoids which is the best dose for the individual patient [75]. However, it is not clear if such an approach can minimize the risk/benefit ratio in an individual patient. Also, the way to determine the best dose is empiric.

Table 4 What we know and do not know about glucocorticoids in sarcoidosis

What we know
Prednisone and prednisolone are effective in improving pulmonary function and chest x-ray in acute pulmonary disease.
What we do not know
What is the initial dose for treatment of pulmonary disease?
What is the initial dose for extra-pulmonary disease?
What is the chronic dose for pulmonary and extra-pulmonary disease?
How long should patients be treated?
How should patients be withdrawn from therapy?
How can one determine if there is a "best dose" of prednisone which minimizes risk and provides benefit for the individual patient?

In a retrospective analysis of patients seen at one institution, acute decompensation associated with a drop in the FVC responded within 3 weeks to prednisone [25]. The average dose of prednisone to treat these events was 19 mg, with some variation from 10 to 40 mg a day dosing. While some cases demonstrated a worsening of chest x-ray with the acute event and an associated improvement with therapy, the changes in FVC were more sensitive to change in patients symptoms.

The use of prednisone for extra-pulmonary disease has rarely been studied in a systematic fashion. There are no randomized control trials to evaluate such treatment. One controversy is the dosage of initial therapy for treatment of extra-pulmonary disease. Neurologic disease seems refractory to traditional doses of prednisone, so initial therapy is often as high as 80–100 mg of prednisone a day [76, 77]. A similar recommendation of initial high-dose glucocorticoids had been made for cardiac sarcoidosis [78]. However, a retrospective study from Japan found no difference in clinical response in cardiac sarcoidosis for those started on more than 30 mg a day prednisone versus those treated with a lower dose [79]. The response rate for glucocorticoids also seems to vary from organ to organ and for expected outcome For example, prednisone has been reported as effective in treating cutaneous sarcoidosis [80]. However, in a retrospective study of treatment of lupus pernio with prednisone, less than half of patients had total resolution of their disease [48].

Other Glucocorticoids High-dose intravenous methylprednisone with doses of up to 30 mg/kg for 1–5 days has been commonly recommended for treatment of refractory neurosarcoidosis [76, 81]. This pulse therapy weekly for 6 weeks has been tested in pulmonary sarcoidosis as well [82]. While patients had a more rapid response to pulse

therapy, eight of the 12 patients relapsed within a year of stopping therapy. Also, there was no difference in clinical status before and 1 year after pulse therapy. Therefore, pulse therapy may be useful to induce a rapid remission of disease, but patients must be maintained on therapy to prevent relapse.

Topical glucocorticoids have been used for skin, eye, and pulmonary disease [83, 84]. These regimens are associated with less complications than systemic glucocorticoids. However, they can still lead to toxicity, including cataracts and glaucoma for patients taking topical glucocorticoids for eye disease [85]. Inhaled budesonide has been shown effective in maintaining an oral prednisolone-induced remission of pulmonary sarcoidosis in one large placebo-controlled study [86]. This was confirmed by another placebo-controlled trial [61]. However, another study found no difference from placebo for treating pulmonary sarcoidosis with inhaled budesonide [62]. Inhaled fluticasone was not found to be superior to placebo for the treatment of acute [53] or chronic [63] pulmonary sarcoidosis. In one study, there was a reduction in cough symptoms, without a change in forced vital capacity of chest x-ray [53].

Acthar Gel The effectiveness of adrenocorticotropic hormone (ACTH) for sarcoidosis was described in the early 1950s [66, 67]. The drug requires systemic administration and seemed to rely on adrenal cortex responsiveness. With the development of prednisone and other direct glucocorticoids, Acthar gel became much less used. However, there has been some evidence that Acthar gel stimulates multiple melanocortin receptors (MCRs) [87, 88]. The stimulation of these MCRs may lead to immunosuppression beyond the effect on cortisol stimulation. The drug has been shown to be effective when given twice a week [89]. During this time, the serum cortisol only rose for 12–24 h after administration and then returned to normal. This may lead to less toxicity then daily high-dose prednisone. The drug therefore seems to have potential role as an alternative in refractory sarcoidosis [90].

Non Steroidal Agents Several drugs have been studied as potential steroid sparing or steroid alternatives in sarcoidosis. Table 5 summarizes the evidence for use of many of these drugs when used to treat pulmonary disease. The results were usually reported in terms of changes in FVC, DLCO, or chest x-ray. Other parameters, such as changes in 6-min walk distance and quality of life measurements, have been used less frequently.

Anti-Metabolite Therapy

Methotrexate is the most commonly used cytotoxic immunomodulator in sarcoidosis [105]. This is in part due to the large number of trials supporting its use for both pulmonary and extrapulmonary disease. There remain several unanswered questions regarding the use of methotrexate for sarcoidosis. The initial dose of the drug varies, although most studies used between 5 and 15 mg once a week [10, 50, 91]. The duration of therapy is also unclear, although most studies discuss prolonged use for patients who have relapsed when initial therapy was withdrawn [10]. A recent consensus statement was published regarding recommendations for monitoring for toxicity in sarcoidosis [106]. This statement suggested monitoring a complete blood count and liver function testing every 1–3 months for patients receiving methotrexate therapy. While methotrexate can lead to liver damage, routine liver testing appears an adequate method to detect toxicity [107]. The dose of methotrexate appears to be the same for cutaneous, ocular, and neurologic disease as that used for pulmonary disease [10, 108, 109].

Leflunomide is a methotrexate analogue associated with less gastrointestinal and pulmonary toxicity than methotrexate. It has been reported as effective in treating pulmonary and extra-pulmonary disease [95, 110]. The dose for all manifestations is 10–20 mg daily. Monitoring is similar to methotrexate, since toxicity is similar to that drug [111]. However, leflunomide can rarely cause peripheral neuropathy, so patients should be asked about this unusual but important complication [112].

Azathioprine is another cytotoxic agent used in sarcoidosis. Open-label trials have demonstrated benefit in some but not all cases [94, 113]. It has also been reported as effective in neurosarcoidosis [114]. In a recent retrospective analysis of two centers, azathioprine was associated with a similar rate of response as methotrexate. However, it was found that azathioprine led to a significantly higher rate of infections during therapy [9]. The increased toxicity of azathioprine versus methotrexate has been noted in other conditions [115]. Patients on azathioprine should be monitored regularly for leukopenia due to treatment [111].

Mycophenolate has been reported as effective in treating pulmonary and neurologic disease [97, 116]. The usual dose is 500–1500 mg twice a day. Gastrointestinal symptoms are the usual dose-limiting complication. Patients on mycophenolate should be monitored with complete blood counts on a regular basis [111].

Biologic Agents

Anti-TNF Agents The anti-TNF monoclonal antibodies have changed the approach to chronic sarcoidosis [117]. These agents have been reported effective in patients with refractory neurologic [116, 118], ocular [99, 119], and skin [48] manifestations. For chronic pulmonary disease, case series have reported benefit for both infliximab [33, 120, 121] and adalimumab [122]. Two double-blind, placebo-controlled trials demonstrated significantly more improvement in FVC with infliximab but not seen with placebo [16, 17].

Table 5 Evidence to support the use of non-steroidal immunosuppressant therapy for pulmonary sarcoidosis: improves lung function or chest x-ray in symptomatic disease

	DBPCRT	OLRT	Case series
Methotrexate	No		Yes
	Baughman [50] FVC		Lower [10] FVC
			Vucinic [91] FVC
Azathioprine			Yes
			Muller-Quernheim [92] FVC, CXR
			Sharma [93] FVC
			No
			Lewis [94] FVC
Leflunomide			Yes
			Sahoo [95] FVC
Mycophenolate			Yes
			Brill [96] FVC
			Hamzeh [97] FVC
Infliximab	Yes		
	Baughman [41] FVC, CXR		
	Rossman [17] FVC, CXR		
Adalimumab		Yes	Yes
		Sweiss [98] FVC	Erckens [99] DLCO
			No
			Milman [100] FVCKamphius
			[101] FVC
Rituximab		Yes	
		Sweiss [102] FVC	
Pentoxifylline	No	Yes	
	Park [103]	Zabel [104]	

However, not all anti-TNF agents have been found to be as effective in sarcoidosis. Etanercept has been reported as effective in some cases of refractory sarcoidosis [123]. However, it was found to have limited benefit for pulmonary disease in an open-label trial [124]. A randomized trial found no difference between etanercept and placebo for chronic sarcoidosis-associated uveitis [49]. This difference in response may be due to the fact that etanercept is a TNF receptor antagonist and therefore may not have as much effect on granulomas and anti-TNF antibodies [125].

Not even the anti-TNF antibodies are equally effective [126]. A recent report of the ineffectiveness of golibmumab for chronic pulmonary sarcoidosis [52] highlights that there may be differences in mechanism in action or differences in pharmacokinetics of these drugs in treating sarcoidosis. This has already been noted in Crohns' disease. Adalibmumab has been reported as effective for pulmonary and ocular disease, but patients usually required a higher loading dose and maintenance dose of adalimumab than that used for rheumatoid arthritis [127, 128]. No such dose modification is needed with infliximab.

These studies have led to several points that clarify what we know and do not know about anti-TNF therapy in sarcoidosis (Table 6). A recent Delphi study tried to resolve some of these issues [117]. As noted, two randomized, placebo-controlled trials demonstrated a benefit for infliximab versus placebo [16, 17]. However, the dose of infliximab and schedule for dosing is unclear. In one study, there was no difference in the response rate for 3 versus 5 mg/kg [16]. However, most clinicians employ a dose of 5 mg/kg [117]. The dosage of adalimumab is even less clear, since much higher doses are used for Crohn's disease compared to rheumatoid arthritis. There was no consensus for the dosing used to treat sarcoidosis [117].

The duration of therapy is also unknown. Discontinuing infliximab treatment in less than a year after starting the drug

Table 6 What we know and do not know about anti-TNF agents in sarcoidosis

What we know
Infliximab is effective for chronic and extra-pulmonary disease.
What we do not know
Is infliximab superior to corticosteroids or only steroid sparing?
Is adalimumab as effective as infliximab when the drugs are given at equivalent doses?
How long should a patient receive anti-TNF therapy?
Should the anti-TNF therapy be tapered off and, if so, how?

had a 50 % or higher chance of their sarcoidosis relapsing [33, 129]. Therefore, many patients are treated for years with the drug. It is unclear how to discontinue the drug. A consensus opinion was to gradually withdraw the drug by increasing the interval between doses [117]. However, there are no clinical trials supporting this approach.

It is unclear whether infliximab and adalimumab are simply steroid sparing or whether they can be considered treatments for steroid-resistant patients. There have been reports that infliximab can be effective in cases where conventional doses of prednisone have failed to control skin or neurologic disease [48, 116, 118]. However, an analysis of the large randomized trial of infliximab versus placebo demonstrated no difference in response versus placebo for those patients treated with 20 mg or more a day of prednisone or its equivalent [20].

Rituximab Another biologic agent reported as effective in refractory sarcoidosis is rituximab [130–132]. This is a monoclonal antibody which depletes CD20+ B cells and this appears to have significant immunomodulatory effects [133]. It has a different toxicity profile than the anti-TNF agents. There is less risk for reactivation of tuberculosis and other serious infections [134]. However, viral and other infections are more likely to occur [135]. The dosing of rituximab is unclear. In one study, all patients received two doses of 1000 mg of rituximab 2 weeks apart and were observed for relapse over the next year [130]. This is the standard regimen used in rheumatoid arthritis. In another study, after initial loading dose, patients were placed on a maintenance regimen similar to that used for lymphoma [131]. It is not clear which regimen is superior.

Approach to Treatment for Pulmonary Sarcoidosis

As noted above, there are limitations to what we know about the best treatment for sarcoidosis. However, sufficient information can be gleaned from the current trials to lead to evidence-based recommendations for treatment of pulmonary sarcoidosis with anti-inflammatory agents [7, 136]. Evidence-based recommendations based on published literature can be graded based on the level of evidence available in the published literature (Table 7) [137]. For sarcoidosis, there is not yet a formal evidence-based recommendation based on an expert panel. We have adapted this level of recommendations to the available evidence to establish our approach to patients.

As discussed above, for those patients with only adenopathy on chest x-ray (scadding stage 1), there is no evidence that treatment will change the outcome (level 1B) [13]. For those patients with parenchymal lung disease and no symptoms, there is evidence to support use of oral and/or inhaled corticosteroids to improve pulmonary function and chest x-ray (level 2B) [15, 86]. However, the toxicity of long-term corticosteroids is often felt to outweigh the potential benefit, so treatment is usually made on a case by case basis.

Figure 3 summarizes the recommendations for treatment for symptomatic pulmonary sarcoidosis patients with parenchymal infiltrates (scadding stages 2–4). For initial therapy of symptomatic pulmonary disease, prednisone at 20–40 mg daily or its equivalent remains the drug of choice [78, 136]. Further treatment depends on the individual patient's response, including intolerance. Prolonged use of glucocorticoids for pulmonary sarocoidosis at a dose of more than 10 mg a day was found to have significantly more side effects than a lower dose [138]. Therefore, most clinicians are comfortable with maintaining on prednisone if the dose can be

Table 7 Grade of evidence-based recommendations based on the level of evidence

Grade of recommendation	Methodological quality of supporting evidence	Benefit versus risk	Implications
1A	RCTs without important limitations or overw helming evidence form observational studies	Benefits clearly outweigh risk	Strong recommendation, can be applied to most patients in most circumstances without reservation
1B	RCTs with important limitations or exceptionally strong evidence form observational studies	Benefits clearly outweigh risk	Strong recommendation can be applied to most patients in most circumstances without reservation
1C	Observational studies or case series	Benefits clearly outweigh risk	Strong recommendation, may change when higher quality evidence becomes available
2A	RCTs without important limitations or overwhelming evidence form observational studies	Benefits closely balanced with risks	Weak recommendation, best action may differ depending on circumstances
2B	RCTs with important limitations or exceptionally strong evidence form observational studies	Benefits closely balanced with risks	Weak recommendation, best action may differ depending on circumstances
2C	Observational studies or case series	Benefits closely balanced with risks	Weak recommendation, best action may differ depending on circumstances

Adapted from Guyatt et al. [137]

RCTs randomized clinical trials

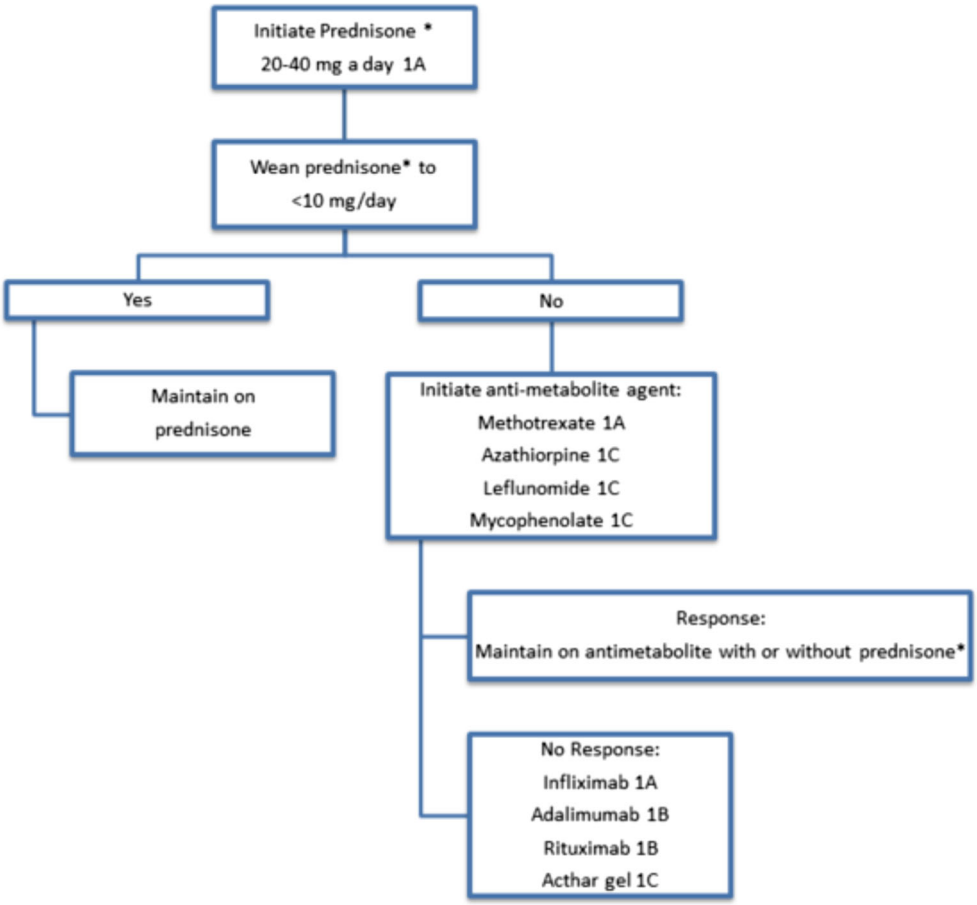

Fig. 3 Recommendations for treatment for symptomatic pulmonary sarcoidosis patients with parenchymal infiltrates (scadding stages 2–4). Level of evidence is indicated for each recommendation using Table 7

tapered to less than 10 mg a day [105]. For those in whom the dose cannot be reduced, the addition of an anti-metabolite is recommended as the next step. As noted above, methotrexate has been the most studied anti-metabolite, with level 1B support of its use in this situation. While all the other anti-metabolites appear to be equally effective, side effects are major consideration for the individual patient. In one study comparing methotrexate to azathioprine, the agents had similar efficacy, but methotrexate was associated with less toxicity [9].

In patients who fail to respond to the addition of anti-metabolite, the next step is usually a biologic agent. Infliximab is the best supported drug, with a leval 1A recommendation. However, there are several reasons why an alternative agent may be employed. Since infliximab is a chimeric antibody, it may lead to significant allergic reactions. In these patients, the humanized antibody adalimumab has been reported as safe in most patients [139]. Prior malignancy, tuberculosis, disseminated fungal infections, or multiple sclerosis are contraindications to the anti-TNF treatments [117]. In that situation, alternative agents such as rituximab or Acthar gel have been reported as effective. Since these agents are all quite expensive, individual treatment regimens may be modified based on the patient's insurance plan.

As noted in Table 1, there are several other causes of dyspnea in the sarcoidosis patients. Many of these do not respond to the anti-inflammatory drugs such as glucocorticoids. Significant complications of pulmonary sarcoidosis that lead to dyspnea are infection and pulmonary hypertension.

Infections of the lower respiratory tract occur often in sarcoidosis patients. These are often acute events and respond to short courses antibiotics with or without glucocorticoids [140]. These are similar to acute exacerbations in patients with chronic bronchitis. These events occur more frequently in patients with bronchiectasis [140] or large-airway disease [141]. Another infectious complication is aspergillus. This can lead to chronic morbidity and some mortality [142, 143]. Treatment of aspergillomas includes systemic anti-fungal agents such as itraconazole and occasional intra-cavitary drug instillation [144].

Treatment of sarcoidosis-associated pulmonary hypertension requires specific therapy for the pulmonary hypertension [145]. In chronically dyspneic patients, up to half of patients will have pulmonary hypertension [146]. While most of these patients have pre-capillary pulmonary hypertension, a significant proportion has left ventricular diastolic dysfunction [147]. The latter has a significantly better prognosis in part because of response to diuretics. Pre-capillary pulmonary

hypertension may respond to pulmonary vasodilators [148, 149]. A recent double-blind placebo-controlled study found bosentan treatment was associated with significant improvement in pulmonary artery pressure while there was no change for the placebo group [150].

Conclusion

Treatment of sarcoidosis must focus on the specific problem for the patient. Anti-inflammatory drugs, especially glucocorticoids, remain the treatment of choice for most patients. Antimetabolites and biologic agents are steroid sparing. Levels of evidence support treatment decisions for many aspects of care for pulmonary disease. Unfortunately, there are few trials specifically designed to examine extra-pulmonary disease. The extrapolation of treatment regimens for extra-pulmonary disease, including dose and duration, is not evidence based in most situations. Future clinical trials will try to address both pulmonary and extra-pulmonary outcomes [151].

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