Chapter 3
The Treatment of Pulmonary Sarcoidosis

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Abstract Decisions regarding treatment of sarcoidosis rely on several factors. These include symptoms, organ involvement, signs of functional impairment, and current and prior therapy. Over the years, the treatment options for sarcoidosis have increased. While this has allowed the clinician to tailor therapy for the individual patient, it also has led to the need to consider risk and benefit each individual patient. Not all therapy is equally effective in sarcoidosis. The benefits from an individual therapy may be more apparent within a few weeks, such as with glucocorticoids and anti-TNF biologic agents, whereas cytotoxic drugs such as methotrexate (MTX) may take up to 6 months or longer to demonstrate their effectiveness. Some drugs such as pentoxifylline seem only to be useful as steroid-sparing agents for pulmonary disease. In addition drugs such as chloroquine and thalidomide may be effective for cutaneous disease but not pulmonary disease.

Keywords Sarcoidosis • Prednisone • Methotrexate • Azathioprine • Leflunomide • Hydroxychloroquine • Infliximab • Adalimumab

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Introduction

Decisions regarding treatment of sarcoidosis rely on several factors. These include symptoms, organ involvement, signs of functional impairment, and current and prior therapy. Over the years, the treatment options for sarcoidosis have increased. While this has allowed the clinician to tailor therapy for the individual patient, it also has led to the need to consider risk and benefit each individual patient.

Not all therapy is equally effective in sarcoidosis. The benefits from an individual therapy may be more apparent within a few weeks, such as with glucocorticoids and anti-TNF biologic agents [1, 2], whereas cytotoxic drugs such as methotrexate (MTX) may take up to 6 months or longer to demonstrate their effectiveness [3]. Some drugs such as pentoxifylline seem only to be useful as steroid-sparing agents for pulmonary disease [4, 5]. In addition, drugs such as chloroquine and thalidomide may be effective for cutaneous disease but not pulmonary disease [6, 7].

Despite our increasing number of agents for treating sarcoidosis, there is evidence to suggest that the rate of hospitalization and death from sarcoidosis is rising [8, 9]. There are several possible reasons for this, including increased recognition of the disease as a cause of mortality, complications of the disease such as pulmonary hypertension [10, 11], and complications of treatment such as infection [12]. As we add more potent treatments, we may be increasing the overall risk for the patient. Another limitation to treatment decisions is the relatively few well controlled double blind placebo-controlled trials [13, 14]. This is in part because of the diverse presentation of sarcoidosis. Nevertheless, evidence recommendations can often be given for individual patient situations [15]. In this chapter, we will review the indications for therapy, current treatment options, and propose guidelines for treatment and monitoring with various agents.

Indication for Therapy

Table 3.1 lists those indications proposed as relative and absolute indications for therapy [16]. For many patients, the decision to treat will be based upon the level of symptoms and presence of functional impairment [17]. This is especially true for pulmonary and cutaneous disease. For example, a small skin lesion on the arm or back may not warrant any treatment. However, lupus pernio and hypercalcemia will often be treated with systemic therapy [18].

Pulmonary disease is the most common manifestation of sarcoidosis. However, not all patients with pulmonary disease require systemic therapy. Dyspnea and cough are the major indications for therapy. In the USA, about half of patients with pulmonary disease require systemic therapy [19, 20]. A smaller percentage of patients seem to require systemic therapy for pulmonary disease in Europe and Asia [21, 22]. However, advanced pulmonary disease is encountered throughout the

Table 3.1 Indications for treatment in sarcoidosis

Absolute	Relative[a]
Neurologic	Pulmonary
Cardiac	Cutaneous
Ocular	Hepatosplenomegaly
Hypercalcemia	Nephrolithiasis
Organ failure[b]	Systemic inflammatory response
	Fatigue
	Small fiber neuropathy and autonomic dysfunction

[a]Treatment indicated if patient symptomatic
[b]Such as renal or liver failure

Table 3.2 Parameters to monitor in pulmonary sarcoidosis

	Validated	Reproducible	Sarcoidosis specific	Low cost
Forced vital capacity (FVC)	3+[a, b]	3+	No	Yes
Forced expiratory volume in 1 s (FEV-1)	3+[b]	3+	No	Yes
FEV-1/FVC	3+[b]	3+	No	Yes
Diffusion lung carbon monoxide (DLCO)	3+[b]	2+	No	Yes
6-min walk distance (6MWD) [29]	2+[b]	1+	No	Yes
Chest X-ray: Scadding [33]	No	1+	Yes	Yes
Chest X-ray: Muers [35]	No	2+	Yes	Yes
HRCT Score [38]	Yes	1+	Yes	No
Positron emission tomography (PET) [40, 130]	No	Not tested	No	No
Saint George Respiratory Questionnaire (SGRQ)	3+[b]	2+	No	Yes
Short form-36 (SF-36)	3+[b]	2+	No	Yes
Sarcoidosis Health Questionnaire [131]	3+	2+	Yes	Yes
King's Sarcoidosis Questionnaire [132]	3+	2+	Yes	Yes
Fatigue Assessment Score [43]	3+	2+	Yes	Yes

Adapted from Baughman et al. [25]
[a]Scale: No, 1–3+, unknown
[b]Not validated for sarcoidosis

world. This includes pulmonary fibrosis, which can lead to significant morbidity and some mortality [23, 24].

For pulmonary disease, several parameters have been proposed to initially assess and monitor disease [25] and are summarized in Table 3.2. These include those obtained with pulmonary function testing, especially the forced vital capacity (FVC). Changes in FVC are the most widely used measure of response to therapy [26]. However, other static pulmonary function tests, including the DLCO may change with therapy [27]. Exercise capacity can be assessed by the 6-min walk test, which allows one to determine the 6-min walk distance (6MWD). While changes in 6MWD may be a reflection of changes in lung function, there are several other factors which can affect 6MWD [28]. These include other conditions such as pulmonary hypertension as well as other factors, such as fatigue [29] and impaired muscle

strength [30]. Full cardiopulmonary exercise testing does provide information not obtained from routine spirometry [31, 32]. However, the variability of performing the test across centers has led to limited use in clinical trials of treatments.

Chest imaging has also been used to assess response to therapy. The Scadding staging system has proved a useful way of characterizing the majority of patients with pulmonary disease [33]. There are problems with reproducibility of the staging system [34]. In addition, most studies fail to show significant changes in stage with therapy. Muers et al. devised a detailed radiographic score similar to what has been used in pneumoconiosis [35]. Significant improvement in the Muers' score were seen with prednisone therapy [27] and infliximab [34] compared to placebo. The Muers' score is time consuming and others have reported that a simple comparison of chest X-ray before and after therapy has been useful [36, 37]. However, this method was not able to differentiate patients treated with infliximab versus those treated with placebo [34].

CT scanning, including high resolution CT (HRCT) imaging, has proved useful in identifying manifestations of sarcoidosis as well as complications of the disease such as bronchiectasis, fibrosis, and aspergillomas. Scoring systems for HRCT have been proposed [38, 39]. To date, no study assessing response to treatment in a systematic way of the utility of HRCT is published.

Positron emission tomography using fluor-18 fluorodeoxyglucose (PET) scanning of sarcoidosis has demonstrated that increased activity may be seen in the lungs with parenchymal lung disease. A negative correlation between $^{18F\text{-}FDG}$ PET activity and FVC has been found [40]. Mostard et al. demonstrated that the severity of the pulmonary involvement, assessed by HRCT features and lung function parameters, appeared to be associated with PET activity in sarcoidosis [40]. The majority of patients with fibrotic changes demonstrated inflammatory activity at pulmonary and extra-thoracic sites. In addition, improvement in lung function and PET activity in the lung has been shown after several treatments [41, 42].

Finally several measures of quality of life (QOL) have been reported in the treatment of sarcoidosis. For the most part, the studies have failed to show convincing evidence of change, but this may be due to study design. Also, many of the questionnaires are not sarcoidosis specific. The fatigue assessment scale (FAS) was developed for sarcoidosis patients [43]. Minimal clinically important differences have been determined for this scale [44]. The FAS scale has been shown to significantly improve with neurostimulants [45] and neurostimulant-like [46] drugs.

Figures 3.1 and 3.2 summarize an approach to treating sarcoidosis. In Fig. 3.1, the level of disease is determined based on pulmonary function studies and level of symptoms. In some cases, patients with normal pulmonary function may still have an advanced level of disease because of extra pulmonary disease, such as ocular or neurologic disease. Also, patients with symptoms and normal lung function should lead to investigation of alternative causes of dyspnea. These would include cardiac or muscle disease or complications such as pulmonary hypertension. Figure 3.2 is a guide to the usual therapy for each of these levels of disease.

	FVC>80%	FVC 60-79%	FVC<60%
No symptoms	A	A	Look for other causes of restriction
Mild/moderate symptoms And/or Significant extra-pulmonary disease	B	B	C
Oxygen supplementation 6 minute walk <150 m	Look for alternative causes*	C	D
Significant neurologic or cardiac disease	D	D	D

Fig. 3.1 The level of disease is determined based on pulmonary function studies and level of symptoms. In some cases, patients with normal pulmonary function may still have an advanced level of disease because of extra pulmonary disease, such as ocular or neurologic disease. Also, patients with symptoms and normal lung function should lead to investigation of alternative causes of dyspnea. *Alternative causes would include cardiac or muscle disease or complications such as pulmonary hypertension

Level of Disease	Standard Therapy	May Consider
A	No treatment	Inhaled corticosteroids or NSAIDs
B	Oral corticosteroids	Anti-malarial drugs Cytotoxic agents for patients with persistent disease or steroid associated toxicity
C	Low dose oral corticosteroids and/or cytotoxic therapy	Combination cytotoxic therapy Use of biologic agents for patients with chronic symptoms and/or treatment associated toxicity
D	Anti-TNF-alpha therapy plus cytotoxic therapy and/or low dose corticosteroids*	Other biologic agents Referral for lung transplant if no response to therapy

Fig. 3.2 A guide to the usual therapy for each of these levels of disease determined in Fig. 3.1. *Anti-TNF agents should be used in caution in patients with moderate to severe cardiomyopathy

Individual Treatments

Glucocorticoids: The most widely used treatment for sarcoidosis remains glucocorticoids [47]. This is based on the observation that these drugs can be quite effective for the disease. In addition, several trials have demonstrated a significant improvement in FVC, DLCO, or chest roentgenogram [27, 48]. The drug has also been used effectively in all other manifestations of sarcoidosis, including neurologic [49], cutaneous [18], cardiac [50], and ocular disease [51].

Several case series have demonstrated that corticosteroids are the preferred first drug for sarcoidosis patients. The overall frequency of initial corticosteroid therapy use is about 50 %, but varies from 30 to 80 % (Fig. 3.3) [20, 52–54]. In addition, some underlying conditions may be more likely to treat with corticosteroids. For example, neurological and cardiac involvement is almost always treated initially with corticosteroids. In one report of a large sarcoidosis population in the USA, the most common reason to use corticosteroid therapy was cardiac disease, while lung disease was the third most common, even though the overall prevalence of pulmonary disease was 18 times higher than cardiac disease [19]. For patients with cardiac or neurologic disease, a combination of corticosteroids and cytotoxic agents (such as MTX or azathioprine) are often used for initial therapy, although there is no specific trial demonstrating superiority of this approach over corticosteroids alone.

A bigger question is what dose to begin therapy. The usual dose is 20–40 mg a day. Tapering of corticosteroids is often over a prolonged period. One group did demonstrate a more rapid response to lower doses of prednisone and usually tapered over 2–6 weeks. However, this was more for an acute decompensation of the disease,

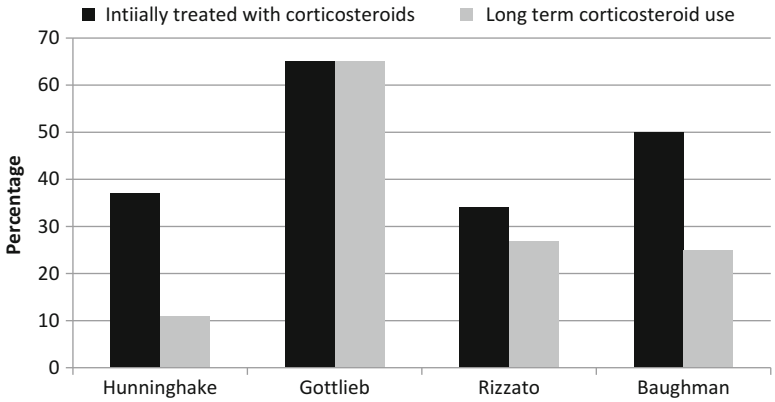

Fig. 3.3 Percentage of patients treated with corticosteroids within the first 6 months of diagnosis and percentage of overall patients who were on corticosteroids long term (at least 2 years from initial evaluation) [20, 52–54]

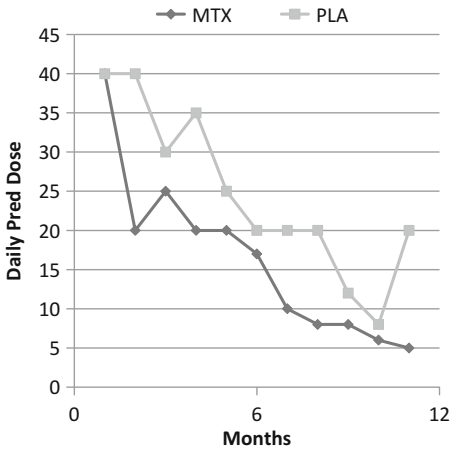

Fig. 3.4 Average prednisone dose at various time intervals for patients with acute pulmonary sarcoidosis receiving either placebo or methotrexate. There was a significant difference in the average prednisone dose after 6 months of therapy [59]

not for standard management of the underlying condition. Figure 3.4 demonstrates the average daily prednisone dosage from one study comparing MTX to placebo for acute pulmonary sarcoidosis. The dose of prednisone was reviewed every 1–2 months, but significant reduction was not seen until 6 months of therapy. After that point, half of the placebo patients required an increase in their prednisone dosage.

The approach to reduction of prednisone is almost as variable as the initial dose. In one multicenter trial, a steroid-tapering regimen was proposed and was able to be applied to over 80 % of visits. A modified version of this schedule evaluates the patient after the first 6–8 weeks of therapy. If the patient has improved, the dose of prednisone is halved. If the patient is stable, the dose is not changed for another 6–8 weeks. At the next and all subsequent visits, the dose is halved if the patient is stable or improved. If the patient relapses, the dose is doubled. For patients in whom the dose cannot be kept below 10 mg within 4–6 months, a steroid sparing alternative is added.

Unfortunately, once a patient begins corticosteroids, they may require long-term treatment. Figure 3.3 also demonstrates the percentage of patients who require long-term therapy in four large studies [20, 52–54]. These studies highlight that there is a subset of patients with chronic disease who are often considered for steroid sparing agent. These would be for patients with level B, C, or D symptoms. At most sarcoidosis centers, these patients represent the majority of patients who are still being followed 2–5 years after their initial diagnosis [55].

The toxicity of prednisone includes weight gain, mood swings, diabetes, cataracts, glaucoma, acne, and increased bruising. Osteopenia and osteoporosis are particular problems with long-term glucocorticosteroid use. Guidelines for preventing osteoporosis have been proposed by the American College of Rheumatology. These include supplemental calcium and vitamin D for sarcoidosis patients; there is an increased rate of hypercalcemia and hypercalcuria based on autonomous 1-alpha hydroxylase activity in the granulomas and increased levels of 1,25-diOH-vitamin D3, especially in patients with chronic sarcoidosis [56]. Therefore, modifications of the ACR recommendations have been made and are summarized in Table 3.3 [57].

Table 3.3 Recommendations regarding osteoporosis prevention for sarcoidosis patients on chronic corticosteroid therapy

- Obtain baseline bone density
- Check serum calcium and 25-OH and 1,25-di[OH]-vitamin D3 levels
- If bone density normal
  - Serum calcium and 1,25-di[OH] low
    (a) Calcium and vitamin D supplement
  - Serum calcium normal and 1,25-di[OH] normal or elevated
    (b) Calcium supplement alone
  - Serum calcium elevated or history of hypercalcemia or hypercalcuria[a]
    (c) No calcium or vitamin D supplement
- If bone density low treat with bisphosphonate and
  - Serum calcium and 1,25-di[OH] low
    (a) Calcium and vitamin D supplement
  - Serum calcium normal and 1,25-di[OH] normal or elevated
    (b) Calcium supplement alone
  - Serum calcium elevated or history of hypercalcemia or hypercalcuria[a]
    (c) No calcium or vitamin D supplement

Adapted from Sweiss et al. [57]

[a]Patients with history of nephrocalcinosis should have 24-h urine to look for hypercalcuria

Methotrexate: This drug is the most commonly prescribed steroid-sparing cytotoxic agent for chronic sarcoidosis [47]. Initial reports suggested approximately two-thirds of patients will respond to the drug after 6 months of therapy [58]. It has been shown to be steroid sparing as compared to placebo in a double blind placebo-controlled trial [59]. The drug has been reported as effective in pulmonary [58], cutaneous [60], ocular [51], and neurologic disease [49]. Guidelines for MTX dosage and monitoring have mostly derived from those developed for rheumatoid arthritis and psoriasis. However, since bone marrow involvement is common in sarcoidosis [61], the dose used in sarcoidosis is often only 10–15 mg a week. In some cases, we have used as little as 2.5 mg a week in patients with significant leukopenia due to their sarcoidosis. In addition, liver involvement is common in sarcoidosis. Surveillance liver biopsies have been performed in sarcoidosis patients on prolonged courses of MTX [62]. However, it appears that routine liver function testing can be useful to detect potential MTX hepatotoxicity. This is especially true with changes in the transaminase levels over time. Folic and folinic acid supplementation may be useful to reduce MTX toxicity [63, 64]. Dosage and evidence-based recommendations for monitoring while prescribing MTX is provided in Table 3.4. These recommendations have been adapted from those made by an expert panel [65].

Table 3.4 Evidence-based recommendations for use of pharmacologic therapy for sarcoidosis

Cytotoxic agents			
Azathioprine	50–200 mg oral daily	*Monitoring blood work*: Complete blood count and hepatic function should be monitored every 1–3 months as long as patients are on therapy *Monitoring of drug clearance*: Measurement of TPMT is useful to detect patients at risk for leucopenia from azathioprine, especially those who will receive higher doses or have a history suggestive of TPMT deficiency [133]. The dose may need adjustment according to creatinine clearance *Monitoring for drug/drug interaction*: Allopurinol inhibits the xanthine oxidase pathway. Patients should not receive azathioprine if they are on allopurinol	For patients who will undergo concurrent therapy with azathioprine and allopurinol, a reduction in dose of azathioprine is recommended. (Grade 1A) For patients who undergo azathioprine therapy, obtaining complete blood counts and renal/hepatic profiles every 1–3 months is recommended. (Grade 1B)
Cyclophosphamide	50–200 mg oral daily OR 500–1,500 mg intravenously every 2–4 weeks	*Monitoring blood work*: A complete blood count and creatinine should be obtained when commencing cyclophosphamide therapy and repeated at least every 4–6 weeks. Patients treated with intermittent intravenous dosing should have a complete blood count prior to the next intravenous dosing. Urine analysis should be performed every 4–8 weeks to look for evidence of hemorrhagic cystitis. In patients with persistent, unexplained hematuria, cystoscopy should be strongly considered to evaluate for possible bladder cancer. Since CYC can induce sterility in men and women, counseling regarding ovarian and/or sperm harvesting prior to initiation of therapy should be considered. In women, gonadotropin releasing hormone given prior to initiation of CYC may prevent premature menopause *Monitoring of drug clearance*: Cyclophosphamide is cleared by the kidneys and direct toxicity to the bladder is the proposed mechanism for hemorrhagic cystitis and bladder cancer. Patients should be well hydrated on the day of dosing, with the recommendation of eight glasses of water as a rule of thumb. For patients at risk for bladder toxicity, co-administration of MESNA may reduce toxicity *Monitoring for drug/drug interaction*: Cyclophosphamide will cause increased rate of bone marrow suppression when used with other cytotoxic drugs. An increased rate of neutropenia may also be seen when used with rituximab	For patients who will undergo cyclophosphamide therapy, monitoring of complete blood count, renal profile, and urinalysis, at least monthly for dose adjustment is recommended (Grade 1B) For patients who will undergo cyclophosphamide therapy, increased fluid intake (e.g., 2 l in addition to normal intake in adults; additional volume given to children needs to be calculated on the basis of body weight) on the days of therapy is recommended (Grade 1C) For patients who undergo or have undergone cyclophosphamide therapy and develop hematuria, further evaluation is recommended (Grade 1B)

(continued)

Table 3.4 (continued)

Leflunomide	10–20 mg daily	*Monitoring blood work*: A complete blood count, liver function panel, phosphate, and creatinine should be obtained when commencing leflunomide therapy and repeated every 4–6 weeks for the first 6 months of treatment. After 6 months, if stable, these parameters can be checked every 6–12 weeks. Clinical monitoring for infections and signs of hepatoxicity is also recommended. If leflunomide is co-administered with MTX, laboratory should be obtained every 1–3 months on an indefinite basis *Monitoring of drug clearance*: Leflunomide is renally cleared and dose modification should be considered for moderate to severe renal disease. The half-life of the drug is quite prolonged and for patients with toxicity, cholestyramine should be used for rapid elimination *Monitoring for drug/drug interaction*: Leflunomide will interact with MTX and trimethoprim/sulfamethoxazole. However the drugs can be given concurrently, but may require more frequent monitoring of the complete blood count. There is insufficient data for leflunomide, but based on published information regarding methotrexate, screening for the excessive use of alcohol or prior history of hepatitis C is recommended	For patients who will undergo leflunomide therapy, screening for the use of alcohol and chronic viral hepatitis prior to treatment are recommended (Grade 2C) For patients who undergo leflunomide therapy, performance of liver function tests and complete blood counts are recommended (Grade 1C) For patients who undergo leflunomide therapy and develop new or worsening signs or symptoms of lung disease, further evaluation is recommended (Grade 1C) For patients who undergo leflunomide therapy and develop neuropathic symptoms, prompt consideration of discontinuing therapy and washing out with cholestyramine are recommended (Grade 1C)
Methotrexate (MTX)	2.5–15 mg once a week	*Monitoring blood work*: Patients should be monitored with a complete blood count, liver function panel, phosphate, and creatinine when commencing MTX therapy and the tests repeated every 4–12 weeks. Clinical monitoring for infections and signs of hepatoxicity is also recommended. Patients with baseline transminases or bilirubin of greater than three times upper limit of normal should be more carefully monitored and initial dose should perhaps be lower, such as 2.5–5 mg once a week *Monitoring of drug clearance*: MTX is cleared by the kidney and the dose may require modification even with mild renal impairment. Patients with moderate to severe renal impairment (GFR < 30 ml/min) normally should not be treated with MTX. Folic acid supplementation of 1 mg a day has been used *Monitoring for drug/drug interaction*: MTX will interact with leflunomide and trimethoprim/sulfamethoxazole; however the drugs can be given concurrently, but may require more frequent monitoring of the complete blood count. There is also a mild interaction with penicillin-based antibiotics and non steroidals such as naprosyn which can lead to mild elevation (<10 %) of the MTX level. Screening for the excessive use of alcohol or prior history of hepatitis C is recommended	For patients who will undergo MTX therapy, screening for the use of alcohol and chronic viral hepatitis prior to treatment are recommended (Grade 2C) For patients who undergo MTX therapy, performance of liver function tests and complete blood counts are recommended (Grade 1C) For patients who undergo MTX therapy, folic acid supplementation is recommended (Grade 1A) For patients who undergo MTX therapy and develop new or worsening signs or symptoms of lung disease, further evaluation is recommended (Grade 1B) For patients who undergo MTX therapy and develop persistently elevated liver transaminases above their own baseline, cessation of treatment or evaluation by liver biopsy is recommended (Grade 1B) For patients with renal insufficiency, ascites, or pleural effusions who undergo methotrexate therapy, decreased MTX clearance may be present and dose reduction may be required (Grade 2C)

Mycophenolate	500–2,000 mg twice a day	*Monitoring blood work*: Complete blood count should be monitored every 1–3 months as long as patients are on therapy *Monitoring of drug clearance*: Mycophenolate blood levels may be obtained if signs and symptoms of gastrointestinal intolerance develop (e.g., diarrhea). High blood levels suggest that mycophenolate may be a cause of diarrhea *Monitoring for drug/drug interaction*: Live vaccines should be avoided while patients are being treated with mycophenolate. Concomitant use of azathioprine should be avoided	For patients who undergo mycophenolic acid therapy and develop adverse GI affects, including diarrhea, interruption of therapy or reduction in dose is recommended (Grade 1B) For patients who undergo mycophenolic acid therapy and develop signs or symptoms of progressive multifocal leukoencephalopathy, cessation of treatment is suggested (Grade 2C)
Chloroquine/ hydroxychloroquine	Chloroquine 250 mg daily Hydroxychloroquine 200–400 mg daily	*Monitoring blood work*: Studies of chloroquine and hydroxychloroquine therapy have suggested a complete blood count and liver function study initially and every 6–12 months. Patients should undergo an ocular examination at least once a year. Since these drugs can cause heart block and cardiomyopathy, patients with unexplained cardiac symptoms should be considered for echocardiogram and electrocardiogram *Monitoring of drug clearance*: Chloroquine and hydroxychloroquine are both cleared by the kidneys. They have prolonged half-lives (more than 1 month) *Monitoring for drug/drug interaction*: Chloroquine and hydroxychloroquine have potentially significant interactions with D-penicillamine and cimetidine leading to higher levels of drug	For patients receiving hydroxychloroquine and chloroquine an eye examination at least once per year is suggested (Grade 2B)

Adapted from Baughman et al. [65]

Azathioprine: The cytotoxic agent azathioprine was most frequently used as a steroid-sparing agent for solid organ transplantation. It had been reported as effective for pulmonary sarcoidosis [66]. It has been used as an alternative to MTX in chronic sarcoidosis. Some groups use the agent because of familiarity with the drug [47]. Since azathioprine has less hepatotoxicity than MTX, it is often used in treating symptomatic hepatic disease [67, 68]. It also may be an alternative agent for patients who develop pulmonary toxicity from MTX. It is associated with a higher frequency of nausea and leukopenia than MTX [69] and therefore is not a likely candidate when those complications rise from MTX treatment. Azathioprine is associated with an increased rate of skin cancers and infections [70]. In a recent trial of idiopathic pulmonary fibrosis, azathioprine therapy was associated with an increased mortality compared to placebo treated patients [71]. Dosage and evidence-based recommendations for monitoring while prescribing azathioprine is provided in Table 3.4. These recommendations have been adapted from those made by an expert panel [65].

Leflunomide: Developed as an alternative to MTX for rheumatoid arthritis [72], leflunomide has been reported as effective in treating chronic sarcoidosis [73, 74]. In one series, treatment was associated with a significant improvement in forced vital capacity compared to pretreatment values [73]. While the drug has similar toxicity as MTX, the frequency of nausea is less. In addition, pulmonary toxicity is much less frequent with leflunomide, although it can still occur [75]. Leflunomide is associated with systemic hypertension and peripheral neuropathy [75, 76], toxicities not associated with MTX. Dosage and evidence-based recommendations for monitoring while prescribing leflunomide is provided in Table 3.4. These recommendations have been adapted from those made by an expert panel [65].

Mycophenolate: While not as commonly used as other cytotoxic agents, mycophenolate appears to be effective at least in some patients with chronic sarcoidosis. It has been reported in small case reports as effective in treating cutaneous [77], ocular [78], and neurologic disease [79]. While the drug has not been used that frequently in sarcoidosis, it appears to have some advantages over other cytotoxic agents. This includes a lower rate of leukopenia, an important issue in sarcoidosis patients who may have bone marrow involvement from the underlying disease [61, 80]. There is an increased rate of infection and cutaneous malignancies similar to that seen with azathioprine [81, 82]. Dosage and evidence-based recommendations for monitoring while prescribing mycophenolate is provided in Table 3.4. These recommendations have been adapted from those made by an expert panel [65].

Antimalarial agents: Chloroquine and hydroxychloroquine represent the two antimalarial drugs that have been used in treating sarcoidosis [6, 83]. These agents have been reported as effective in both cutaneous and pulmonary disease. These drugs appear to be more effective for cutaneous than pulmonary disease [6, 84]. However one study did find chloroquine was superior to placebo in treating patients with chronic pulmonary disease [85]. The major toxicity of these drugs is ocular and routine eye examinations are recommended for both agents [86]. Hydroxychloroquine

is associated with low risk of ocular toxicity, especially when low doses that are adjusted for patient's weight are employed [87]. However, eye examinations on a regular basis should still be considered [88]. Dosage and evidence based recommendations for monitoring while prescribing the antimalarial agents is provided in Table 3.4. These recommendations have been adapted from those made by an expert panel [65].

Tumor Necrosis Factor Inhibitors

Tumor necrosis factor (TNF) was found to be secreted in high levels from alveolar macrophages of some patients with sarcoidosis [89]. Alveolar macrophages from patients with chronic sarcoidosis with worsening disease despite corticosteroid therapy still released high levels of TNF [90]. These observations suggested that inhibition of TNF may be a target of therapy in sarcoidosis patients [91]. When the chimeric monoclonal anti-TNF antibody infliximab became available for clinical use, there were a large number of case series demonstrating the effectiveness of some of these drugs in refractory sarcoidosis [92–94]. These drugs proved effective for cutaneous lesions, such as lupus pernio [95], neurologic [96], and other forms of refractory disease [97, 98]. Subsequently, two double-blind placebo were performed. Both of these found infliximab was superior to placebo in treating refractory pulmonary disease [2, 99]. In the larger of these studies, infliximab treatment was also superior to placebo in treating extra pulmonary disease [100]. Dosage and evidence-based recommendations for monitoring for infliximab and adalimumab are provided in Table 3.5. These recommendations have been adapted from those made by an expert panel [65].

Examining the various reports regarding the use of TNF-alpha inhibitors for sarcoidosis, guidelines have been proposed (Table 3.6) [101]. Analysis of the two randomized trials using infliximab for pulmonary sarcoidosis provides some insight regarding who is more likely to respond to treatment. However, these two studies have some major differences. The study led by Rossman included only 19 patients. Analysis was performed after only 6 weeks of therapy. The study led by Baughman consisted of 138 patients. Analysis was performed after 24 weeks of therapy. In the larger randomized trial comparing infliximab to placebo, the median FVC was 69 %. Subgroup analysis of response to infliximab found that those patients with a FVC > 69 % had no significant response to infliximab therapy compared to placebo, while there was significantly larger response for those whose FVC was less than 69 % [2]. In the other randomized trial, there was an even larger response to infliximab compared to placebo (Fig. 3.5). The median FVC for that study was 60 % [99]. These studies support the concept that more severe patients are more likely to respond to therapy.

Not all patients with chronic pulmonary sarcoidosis will respond to infliximab therapy [102]. There is little evidence to support that these drugs would be effective for patients with severe fibrosis [23]. There have been two markers which were

Table 3.5 Evidence-based recommendations for use of biologic agents for sarcoidosis

TNF-alpha inhibitors	Usual dosage	Clinical recommendations	Evidence-based recommendations
Adalimumab Infliximab	40 mg subcutaneously every 1–2 weeks 3–5 mg/kg intravenously initially, 2 weeks later than every 4–8 weeks	*Assessing risk for tuberculosis*: Tuberculin skin testing and chest radiograph should be obtained and reviewed prior to therapy. In addition, one should consider the risk for histoplasmosis, blastomycosis, or coccidioidomycosis for patients living in or visiting endemic areas *Assessing risk for hepatitis*: Hepatitis serology should be obtained prior to onset of therapy. Use of drug should be avoided if active viral hepatitis is present *Monitoring blood work*: Patients with a history of viral hepatitis or chronic carrier states should be monitored for viral hepatitis reactivation as long as patients are on therapy. Anti-dsDNA antibodies can be measured if lupus-like symptoms develop during therapy *Monitoring for drug/drug interaction*: Live vaccines should be avoided while patients are being treated with adalimumab	A chest X-ray is recommended prior to treatment (Grade 1C) A tuberculin skin test is recommended to screen for latent tuberculosis prior to treatment (Grade 1C) For patients with a chest X-ray consistent with prior tuberculosis or a positive tuberculin skin test, and/or are high risk individuals, active tuberculosis infection should be excluded prior to treatment with adalimumab (Grade 1C) or infliximab (Grade 1B) For patients with latent *M. tuberculosis*, active prophylactic treatment following published guidelines before initiation of anti-TNF-alpha therapy is recommended (Grade 1B) For patients with latent *M. tuberculosis*, close monitoring for tuberculosis is recommended for up to 6 months after discontinuing therapy (Grade 1C) For patients who develop symptoms indicative of tuberculosis, prompt evaluation for active disease is recommended (Grade 1C) For patients with known grade III or IV New York Heart Association class heart failure, administration of adalimumab (Grade 1C) or infliximab (Grade 1B) is not recommended For patients with a history of congestive heart failure (CHF) who undergo anti-TNF alpha therapy, close observation for CHF exacerbation is recommended (Grade 1C) For patients with a history of demyelinating disease, administration is not suggested (Grade 2C) For patients with no history of demyelinating disease who experience symptoms or display signs of a demyelinating process, discontinuation of therapy is suggested (Grade 2C) For patients who develop symptoms of a lupus-like disorder, discontinuation of therapy is suggested (Grade 2C) For patients who are at risk for viral hepatitis, serologic screening for hepatitis B is recommended prior to treatment (Grade 1C) For patients who have hepatitis B virus infection, anti-TNF-alpha therapy should not be administered (Grade 1C) For patients who develop unresolved infections, discontinuation of treatment until the infection is resolved is recommended (Grade 1B) For patients who are pregnant, administration of anti-TNF alpha therapy is used only if alternatives are not able to be used (Grade 2C)
Rituximab	1 g intravenously every 2–4 weeks	*Monitoring blood work*: Complete blood count should be checked prior to each treatment. Patients should have serology checked for viral hepatitis prior to initiating therapy *Monitoring of drug clearance*: No specific recommendations *Monitoring for drug/drug interaction*: Rituximab can be used in combination with other immunosuppressive agents and as such additive or synergistic suppression of host immunity particularly lymphocyte-based defenses can occur during use of this agent. There is also the potential for more neutropenia when the drug is given with cytotoxic agents, including cyclophosphamide	For patients who undergo anti-lymphocyte antibody therapy, monitoring for infusion reactions is recommended (Grade 1B)

Adapted from Baughman et al. [65]

Table 3.6 Features predictive of response to anti-TNF therapy for chronic sarcoidosis

Feature	Response	Studies
FVC < 70 %	Increased response compared to placebo of 3.3[a] to 5.9 %	Baughman et al. [2] Rossman et al. [99]
Dyspnea > 1 on Medical Research Council scale	Increased response to compared to placebo 3.8 %[b]	Baughman et al. [2]
Disease duration > 2 years	Increased response to compared to placebo 3.2 %[a]	Baughman et al. [2]
Elevated C reactive protein	Increased response to compared to placebo 5.1 %[b]	Sweiss et al. [103]
Reticulonodular infiltrate on chest X-ray	Patients with >5 % improvement in FVC after treatment: Infliximab: 47 % Placebo: 11 %[a]	Baughman et al. [34]
Lupus pernio	Resolution or near resolution of skin lesions: Infliximab 77 % All other regimens: 29 %[c]	Stagaki et al. [18]
Neurologic disease	Patients failing other regimens all responded	Moravan [79] Sodhi [105]
Chronic ocular disease	Patients failing other regimens responded to either adalimumab or infliximab	Baughman [106] Baughman [51] Erckens [107]
Extra pulmonary sarcoidosis	Patients with chronic extra pulmonary disease more likely to improve with infliximab than placebo based on physician organ specific assessment[c]	Judson [100]

[a]Compared to placebo, $p < 0.05$
[b]Compared to placebo, $p < 0.02$
[c]Compared to placebo, $p < 0.002$

identified retrospectively from a randomized trial of patients with treated with infliximab. An elevated C reactive protein (CRP) was associated with a significantly higher rate of response to infliximab compared to control [103]. Patients with reticulonodular infiltrates on chest roentgenogram were also more likely to respond to therapy [34]. That study also identified a inflammatory profile which was associated with an enhanced response to therapy [104]. These markers need to be studied prospectively before they can be applied in standard practice.

Anti-TNF therapy has been employed in refractory extra pulmonary disease as well. In one study, the overall response of extra-pulmonary disease responded better to infliximab compared to placebo [100]. That study employed a physician assessment of each organ and comparisons were made before and after therapy. Specific organ involvement has also been reported. In a study of over a hundred treatment regimens for patients with *lupus pernio*, Stagaki et al. found that infliximab was associated with significantly higher rate of resolution or near completed rate of resolution compared to any other regimen employed [18]. In patients with

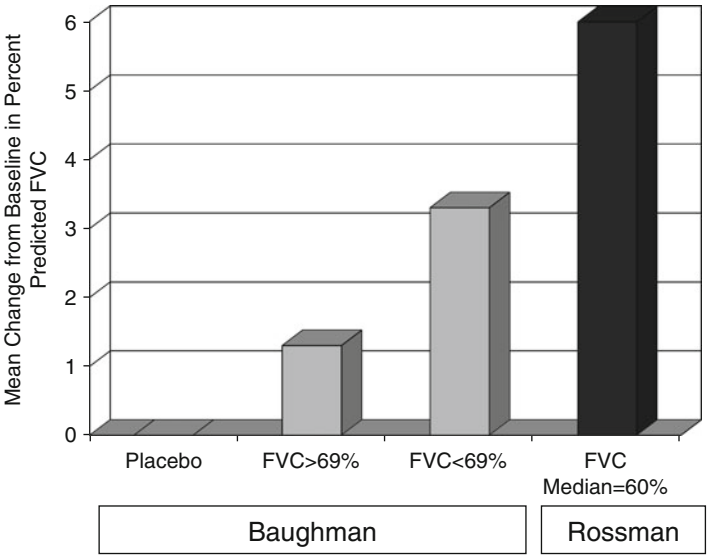

Fig. 3.5 The mean change in FVC compared to placebo after 6 weeks (Rossman) or 24 weeks (Baughman) of therapy [2, 99]. For Baughman study, the study median was 69 %. For those patients whose pretreatment FVC was less than 69 %, there was a significant change in FVC compared to placebo ($p<0.05$)

refractory neurosarcoidosis failing other regimens, two case series reported responses in all patients treated with infliximab [79, 105]. For ocular sarcoidosis, both infliximab [51, 106] and adalimumab [51, 107] have been reported as successful in treating patients who have failed other regimens.

Other Agents

Rituximab has been reported as effective in treating refractory cases of sarcoidosis. These include joint and eye disease [108, 109]. It is a monoclonal antibody which leads to B cell depletion and has proved useful in treating refractory rheumatoid arthritis [110]. It has a significantly different toxicity profile than the TNF-alpha inhibitors. Dosage and evidence-based recommendations for monitoring while administering rituximab is provided in Table 3.5. These recommendations have been adapted from those made by an expert panel [65].

The phosphodiesterase 4 (PDE-4) inhibitors have been reported as effective in some cases of sarcoidosis. These drugs inhibit TNF release by alveolar macrophages [111, 112]. Pentoxifylline was the first drug in this class reported as effective in treating sarcoidosis [113]. In a randomized, placebo-controlled trial, pentoxifylline was steroid sparing compared to placebo, but was not associated with significant improvement in lung function [5]. Aprelimast is a more selective PDE-4 inhibitor.

In an open label trial of chronic cutaneous sarcoidosis, it was shown to be effective [114]. The major toxicity of this class of drugs has been nausea and tachycardia.

The antioxidants may have a role in treating some patients with sarcoidosis. Quercetin has been shown to reduce oxidant stress in sarcoidosis patients [115]. Its role in improving outcome in sarcoidosis is currently under study. Another antioxidant, *N*-acetyl cysteine (NAC), has been suggested as a potential treatment for pulmonary fibrosis. This was based on its effectiveness as a supplemental agent to azathioprine in patients with idiopathic pulmonary fibrosis [116]. The effectiveness of NAC in the treatment of sarcoidosis is also under study.

Special Considerations in Sarcoidosis

There are several clinical problems associated with sarcoidosis which do not always respond to just anti-inflammatory therapy. These conditions may respond to specific therapy for these complications. However, that specific therapy may not be effective for other aspects of the disease. Examples of this include sarcoidosis associated pulmonary hypertension, fatigue, and small fiber neuropathy. For all three of these conditions, alternative therapies have been reported as effective.

Sarcoidosis-associated pulmonary hypertension (SAPH) can occur in 5–15 % of unselected sarcoidosis patients an up to 50 % of persistently dyspneic sarcoidosis patients [10, 117, 118]. As noted in Fig. 3.1, SAPH can lead to hypoxia and/or significant dyspnea in patients with normal pulmonary function studies and no evidence of parenchymal lung disease. Diagnosis and treatment of this condition will be discussed elsewhere in this book.

Significant fatigue associated with sarcoidosis has been reported in over half of patients [119–121]. It may occur for years after all other evidence of disease activity has resolved [122]. In some cases, the fatigue may be due to sleep disturbances, which are common in sarcoidosis [123, 124]. In some cases, treatment of the underlying disease with TNF inhibitors has improved fatigue [125]. Neurostimulants have been reported as useful in treating sarcoidosis associated fatigue (SAF) [126]. Specific pharmacologic treatment for SAF has been studied using double blind, crossover design studies. The neurostimulant D-methylphenidate was found to be superior to placebo in treating SAF [45]. In that study, patients were receiving one or more systemic therapy for their sarcoidosis but still had clinically significant fatigue. In another report, r-modafinil was found to be superior to placebo in treating SAF [46]. That study found that there was no difference in improvement for fatigue in those patients with daytime hypersomnulence versus those without, as assessed by multiple sleep latency time. This would suggest these neurostimulants work for fatigue in patients with or without sleep disturbance.

Small fiber neuropathy is a clinical problem encountered in sarcoidosis [127]. Intravenous immunoglobulin therapy was reported as effective in a small case series [128]. A recent report suggests that ARA 290 may provide a novel solution to this problem [129].

Recently, Heij et al. demonstrated in a pilot study that ARA 290 reduced small fiber neuropathy-related symptoms including fatigue, autonomic dysfunction, and pain. ARA 290 (a peptide designed to activate the innate repair receptor that arrests injury and initiates cytoprotection, anti-inflammation, and healing) reduces allodynia in preclinical neuropathy models. Moreover, they found a significant improvement from baseline in the pain and physical functioning dimensions of the SF-36 QOL questionnaire [129].

Conclusion

While not all patients with sarcoidosis require treatment, a significant percent of patients do require systemic therapy. An approach to treatment based on lung function and other relevant clinical parameters including and the level of symptoms (see also Fig. 3.1) can lead to a step wise approach to therapy (Fig. 3.2). In patients placed on systemic therapy, the treating physician must monitor for toxicity.

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