

Therapy for sarcoidosis: evidence-based recommendations

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The options for treatment of sarcoidosis have expanded. In this article, we outline a stepwise approach to treatment. Recommendations for treatment are based on available evidence. While corticosteroids remain the treatment of choice for initial systemic therapy, other agents have been shown to be steroid sparing, and therefore useful for long-term management. In addition, new agents have proved to be useful for patients with refractory disease.

KEYWORDS: azathioprine • infliximab • methotrexate • prednisone • sarcoidosis

The clinical outcome of pulmonary sarcoidosis is quite variable. While some patients will undergo spontaneous resolution, other patients will develop chronic, progressive disease [1]. Individual series of cases of sarcoidosis have found that the need for systemic therapy ranges from 20 to 70% of patients [2–5]. Of those patients who have commenced therapy, at least half appear to require systemic treatment for more than 2 years [4,6]. This difference in outcome for sarcoidosis has led to three proposed outcomes of the disease: acute, chronic and refractory [7,8].

Acute disease usually resolves within 2 years, whether the patient is treated or not. The presentation of hilar adenopathy alone is associated with a greater than 80% chance of resolution of lung disease within 2 years [8]. The combination of erythema nodosum and chest radiograph demonstrating hilar adenopathy was reported by Löfgren as highly specific for sarcoidosis and was associated with a good clinical outcome within months of onset of disease [8]. In more recent detailed analysis, it was demonstrated that Swedish sarcoidosis patients with the HLA *DRB1*03* had an excellent prognosis. However, approximately half of patients with Löfgren's syndrome who were *DRB1*03* negative required systemic therapy for more than 2 years after initial diagnosis [9]. This analysis supports previous studies on other European populations [10–12]. Another factor associated with a good prognosis is patients not requiring systemic therapy within the first

6 months of diagnosis. While these patients in general do well, approximately 10% will need long-term systemic therapy [4,6]. These studies indicate that no single factor can be used to predict the long-term outcome of sarcoidosis patients.

The majority of chronic patients can be maintained on a relatively low-dose immunosuppression regimen [13]. Several conditions are associated with chronic disease [8,14]. However, a subset of patients require more aggressive treatment. In a recent survey of sarcoidosis clinics across the world, this represented approximately 10% of all patients who were still being seen 5 years after their original diagnosis [15]. These refractory patients require a detailed evaluation for secondary complications of their disease. Patients with lupus pernio [16], certain neurologic manifestations (leptomeningeal or spinal cord involvement) [17] or bronchial stenosis [18] are more likely to fit into this group.

The management of pulmonary sarcoidosis therefore depends on the level of disease and the symptoms of the patient. Evidence-based recommendations have been made regarding therapy [19–22]. The various articles published in this area have led to some differences in recommendations. This is, in part, due to limitations of data. For example, a meta-analysis of the utility of corticosteroids for sarcoidosis was limited by the combination of studies with short versus long treatment and variable duration of follow-up [20]. Nevertheless, some

recommendations have been made that are supported by the available data. The results of many of the studies for treatment of sarcoidosis with corticosteroids or other agents are summarized in TABLE 1. Most of these studies used forced vital capacity, diffusion lung for carbon monoxide and/or chest radiograph as their end point. In some cases, the studies were designed to determine if the agent could be steroid sparing. FIGURE 1 summarizes the recommendations for treatment for various aspects of disease based on these studies.

Management of stage 0/1 disease

Scadding proposed a staging system for the chest radiographs of sarcoidosis patients [23]. The staging has been widely used over the past 50 years. Stage 1 involves hilar adenopathy alone, stage 2 is hilar adenopathy plus infiltrates, stage 3 is infiltrates alone, stage 4 is fibrosis and stage 0 is no adenopathy, infiltrates or fibrosis. This system has been useful in characterizing the majority of chest radiographs of sarcoidosis patients in large epidemiologic studies [2,24,25].

Patients with stage 0 or 1 chest radiographs are felt to have no parenchymal lung disease and, as such, treatment recommendations are different from those with parenchymal disease (stage 2, 3 or 4). FIGURE 1 summarizes the recommendations for those patients with stage 0 or 1 disease [19].

For the asymptomatic patient with stage 0 or 1 disease, there is strong evidence that no treatment is required [22]. In a double-blind placebo-controlled trial, there was no benefit of corticosteroid therapy versus placebo for patients either during treatment or during the 5-year follow-up [26]. Patients with stage 1 disease have a high rate of resolution of their chest radiograph over the next 2 years, even if they are not treated [8]. Long-term follow-up of these patients reveals that >95% will have a normal chest radiograph within a decade of diagnosis [25].

While asymptomatic patients with stage 0 or 1 disease have a good prognosis, there are some patients with no parenchymal lung disease who are still symptomatic [27]. There are several reasons why these patients may be symptomatic. The first is that the patient may have parenchymal lung disease that is not detected by chest radiograph. The Scadding staging system has some variability and, therefore, there may be disagreement about the presence or absence of parenchymal disease [28]. Computed tomography is more sensitive to parenchymal disease [29]. In a study of ocular sarcoidosis patients, the presence of changes on CT scan were more sensitive than plain chest roentgenogram in predicting who would have a diagnostic bronchoscopy. Patients may also have airway

obstruction due to proximal bronchial stenosis not detected by chest roentgenogram [18].

Other conditions that can lead to dyspnea in sarcoidosis patients include left ventricular dysfunction, muscle disease and fatigue. Sarcoidosis patients with pulmonary hypertension may have a stage 0 or 1 chest radiograph [30,31]. In these patients, the most likely reason is the presence of granulomatous vasculitis in either the arterial or venous side [32]. FIGURE 2 demonstrates the chest roentgenogram of a sarcoidosis patient with persistent dyspnea. The chest radiograph appears to be normal. A right heart catheterization revealed moderate pulmonary hypertension with a normal pulmonary artery occluding pressure. Spruit *et al.* correlated increasing quadriceps muscle weakness with increased dyspnea [33]. His group was subsequently able to demonstrate that focused pulmonary rehabilitation improved dyspnea. Diaphragm muscle involvement has been reported in sarcoidosis and this can lead to dyspnea [34]. Neurologic disease can also lead to respiratory failure [35]. Fatigue is a common complaint in sarcoidosis [36]; increasing fatigue has been shown to be associated with increasing dyspnea and reduced 6-min walk distance [37].

For the symptomatic patients with stage 0 or 1 disease, one must consider these alternative causes. If these have been excluded, one can consider treating these patients for pulmonary sarcoidosis. The same recommendations for patients with stage 2–4 disease should be used. In this situation, one would assume that one is treating undetected parenchymal disease.

Table 1. Outcomes measured in trials of agents for pulmonary sarcoidosis.

Drug	Design	n	FVC	DLCO	Chest radiograph	Steroid-sparing effect	Ref.
Prednisone	DBPCRT	51			Better		[99]
Prednisone	DBPCRT	83	Better		Better		[100]
Prednisone	DBPCRT	37	Better	Better	Better		[101]
Prednisone	DBPCRT	135			NS		[102]
Prednisone	OLRT	58	Better	Better	Better		[5]
Budesonide [†]	DBPCRT	189	NS	Better	Better		[26,39]
Fluticasone	DBPCRT	21	NS		NS	NS	[43]
Methotrexate	DBPCRT	25	NS			Yes	[47]
Azathioprine	OL	11	Better		Better		[55]
Thalidomide	OL	10	NS			Yes	[103]
Cyclosporine	OLRT	37	NS		NS	NS	[104]
Chloroquine	OLRT	18	Better		Better		[81,87]
Pentoxifylline	DBPCRT	27	NS				[87]
Infliximab	DBPCRT	135	Better		Better		[69]
Infliximab	DBPCRT	19	Better		NS		[70]

[†]Patients received 3 months of prednisolone followed by 15 months of budesonide. DBPCRT: Double-blind placebo-controlled randomized trial; DLCO: Diffusion capacity of the lung for carbon monoxide; FVC: Forced vital capacity; NS: Not significant; OL: Open label; OLRT: Open-label randomized trial.

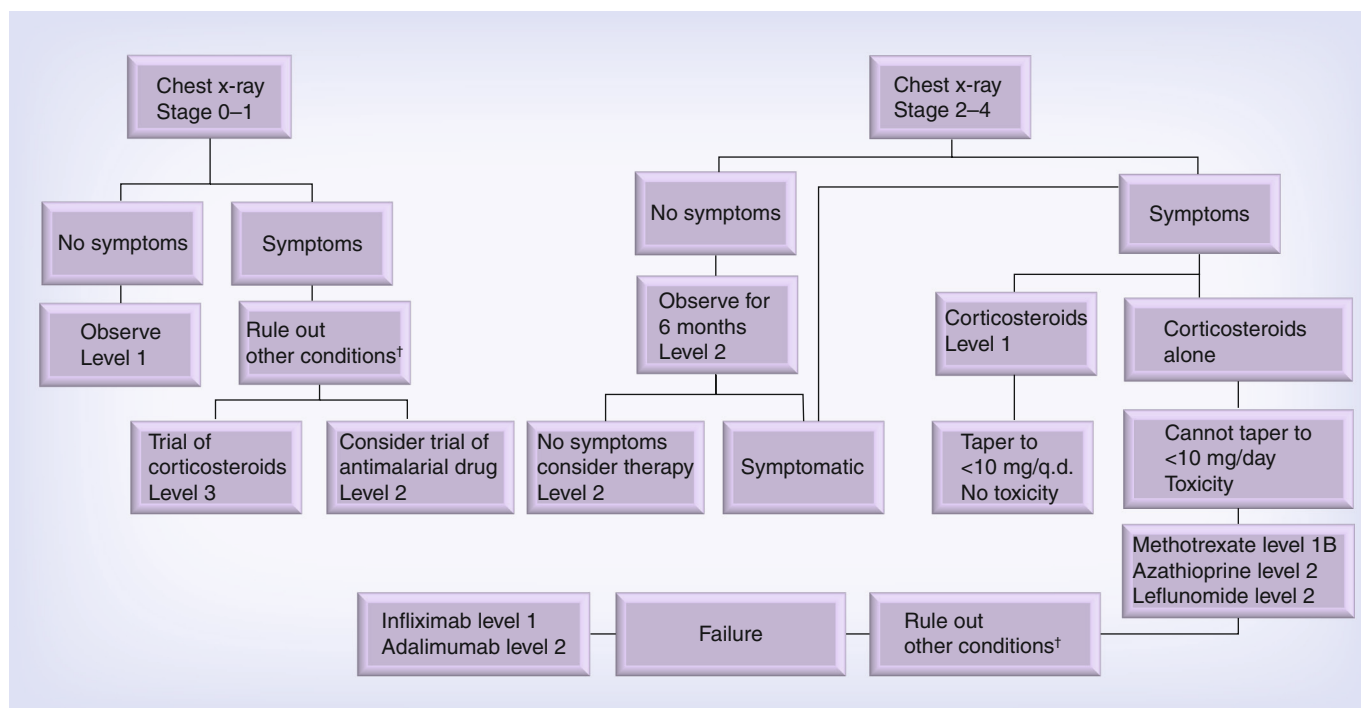


Figure 1. Treatment options for sarcoidosis patients. Level of evidence of recommendations are given.

†Other causes include pulmonary hypertension, congestive heart failure, infection, muscle weakness and fatigue.
q.d.: Once daily.

Management of stage 2–4 disease

Also shown in **FIGURE 1** is the approach for sarcoidosis patients with parenchymal lung disease. For patients with stage 2–4 disease who have no symptoms, the recommendation is observation. **FIGURE 3** summarizes the clinical outcomes observed in one study of sarcoidosis patients with no symptoms at the time of initial evaluation who were observed over the next 6 months [5]. Over 6 months, some patients improved and others became symptomatic. Less than half of the original study patients had persistent infiltrates but no symptoms. For those patients, treatment with 18 months of corticosteroids was associated with a small improvement in lung function. However, it is not clear whether toxicity from 18 months of therapy warranted the small benefit seen with treatment. An alternative to treatment is to continue to observe the patient and only institute therapy if the patient becomes symptomatic. Another alternative is to treat these asymptomatic patients with persistent parenchymal disease with 3 months of systemic therapy followed by 15 months of high-dose inhaled corticosteroids [38].

For those patients with stage 2–4 disease and pulmonary symptoms, there is convincing evidence to support treatment [5,22,39]. The benefit for treatment of these patients is not only an improvement in lung function during therapy [38], but the persistence of these benefits for at least 5 years after therapy is discontinued [39].

For patients treated with corticosteroids, the clinician then tries to minimize the dose of corticosteroids. During withdrawal of corticosteroids, some patients will relapse. For those patients who worsen with withdrawal of corticosteroids, a daily

dose of 20 mg of prednisone has been shown to cause significant improvement in lung function within 3 days [40]. The final dose of corticosteroids will determine the next step in therapy. For some patients, low-dose corticosteroids alone are sufficient to control the disease [13]. Unfortunately, for many patients, the clinician is unable to reduce the dose of corticosteroids to nontoxic levels. While this dose varies from patient to patient, most clinicians feel that the patient should be receiving 10 mg or less of prednisone by month six of treatment [41]. For those patients not successfully tapered, several steroid-sparing alternatives have been considered. **FIGURE 4** shows the results of a Delphi consensus of what would be the first choice of a group of sarcoidosis experts for patients who could not have their prednisone dose tapered [41]. While several drugs were considered, methotrexate was the drug that most physicians use as their preferred steroid-sparing agent. Inhaled corticosteroids improved lung function in asymptomatic patients with stage 2 or 3 disease [38]. However, inhaled steroids do not seem to be effective in symptomatic sarcoidosis patients [42–44].

The evidence to support methotrexate as a steroid-sparing agent includes several case series for pulmonary and extrapulmonary disease [45,46]. There has also been a double-blind randomized trial of methotrexate, which demonstrated that the drug was steroid sparing [47]. Most studies have demonstrated a 60–80% response to methotrexate for pulmonary [45,46], cutaneous [45,46,48], ocular [49–51] and neurologic [17] disease. The drug may take up to 6 months to demonstrate efficacy [52]. Toxicity includes neutropenia and hepatotoxicity. Since sarcoidosis can affect the liver, liver biopsy may be necessary to

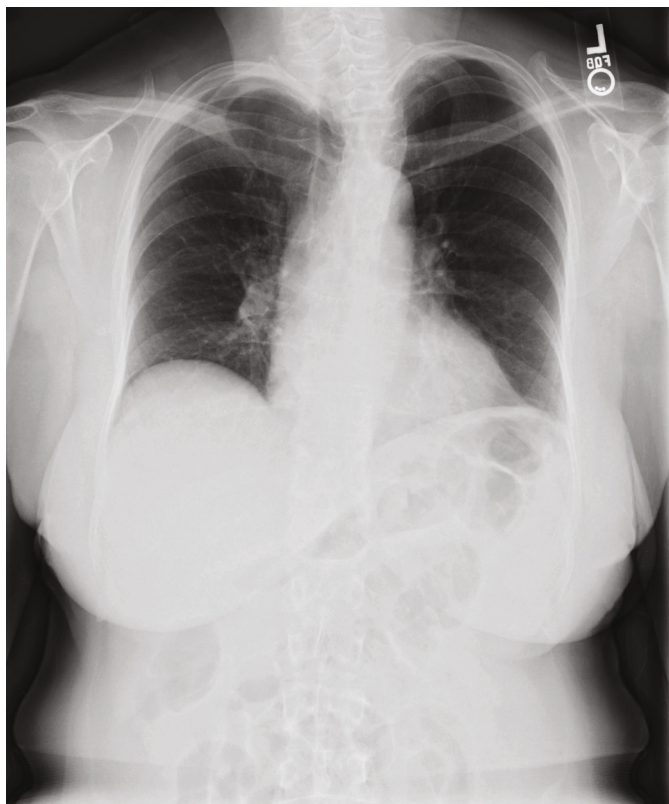


Figure 2. Chest radiograph of a sarcoidosis patient with persistent dyspnea. An echo estimated her pulmonary artery systolic pressure at 82 mmHg. Her right heart catheterization demonstrated a pulmonary artery pressure pressure of 70/40 mmHg, with a mean pressure of 50 mmHg.

determine if a patient has methotrexate hepatotoxicity in cases with abnormal liver function testing [53]. Methotrexate can also lead to pulmonary toxicity [54].

Azathioprine is a commonly used alternative to methotrexate as a steroid-sparing cytotoxic agent. There are few trials published on the effectiveness of azathioprine for sarcoidosis. While some of these have reported a response rate similar to that seen with methotrexate [55,56], others have reported a response rate of less than 30% [57]. Since azathioprine is significantly less hepatotoxic than methotrexate, the drug has been used to treat symptomatic hepatotoxicity [58]. Neutropenia remains a major toxicity factor and monitoring must be performed on a regular basis.

Leflunomide has also been used as a steroid-sparing agent for pulmonary [59,60], cutaneous [60] and ocular [59] disease. The drug is well tolerated and has less toxicity than methotrexate. In two large series, the most commonly cited rationale for using leflunomide was intolerance to methotrexate [59,60]. Leflunomide has also been

used in combination with methotrexate for the treatment of sarcoidosis [59]. In rheumatoid arthritis, treatment with leflunomide plus methotrexate was superior to methotrexate alone [61]. The toxicity profile of leflunomide is similar to methotrexate, except that leflunomide has less gastrointestinal and pulmonary toxicity [62].

There are some patients who continue to have active disease despite the use of these cytotoxic agents, and are considered refractory. This represents at least 10% of chronic sarcoidosis patients [15]. Alveolar macrophages retrieved by bronchoalveolar lavage from refractory patients with progressive disease despite corticosteroid therapy have been found to still secrete high levels of TNF [63]. TNF is a key cytokine in the initiation and perpetuation of the granulomatous response of sarcoidosis.

Over the past 10 years, several monoclonal antibodies to TNF have become commercially available and used to treat sarcoidosis [64]. Initial case series reported a dramatic improvement for patients with pulmonary [65–67], cutaneous [16,65] and ocular [68] sarcoidosis in which other regimens had failed. These observations led to two double-blind randomized trials comparing infliximab with placebo for chronic pulmonary disease [69,70]. In the larger of these trials, infliximab therapy was associated with a significant improvement in forced vital capacity compared with placebo [69]. Rossman *et al.* performed a more limited study of more severe pulmonary disease. They observed a larger response after two treatments with infliximab [70]. The combination of these studies has led to specific recommendations regarding which patients would be most likely to respond to anti-TNF therapy. These are summarized in Box 1. In addition to advanced pulmonary disease, the drug has been reported as effective in patients with chronic cutaneous disease, specifically lupus pernio [16,69,71]. It has also been shown to be effective the treatment for refractory neurologic disease [72,73]. Case series have reported the usefulness of adalimumab for treating refractory sarcoidosis [74–76]. Adalimumab is a humanized monoclonal antibody and has been safely employed in patients who developed allergic reactions to infliximab [77]. It

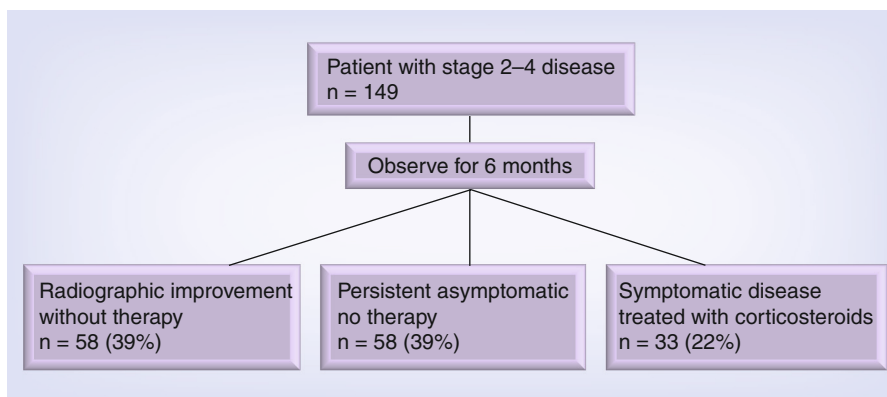


Figure 3. Outcome of 149 asymptomatic sarcoidosis patients with stage 2–4 disease over the first 6 months after initial evaluation. While some patients became symptomatic and required treatment during this time, almost twice as many spontaneously resolved their disease. Data taken from [5].

appears to have a lower rate of response than infliximab [75], but may be more effective if higher doses are employed [78].

Several other agents have been used in patients with sarcoidosis. The antimalarial agents chloroquine and hydroxychloroquine have been reported as useful in treating cutaneous disease [79,80]. They appear to be less effective for pulmonary disease [80]. In one randomized trial of chronic pulmonary sarcoidosis, they had a modest benefit [81]. The antimalarial agents may be useful for selected patients.

Mycophenolate is an immunosuppressant reported as useful in the treatment of several conditions. There have been limited reports of its effectiveness in treating sarcoidosis [72,82,83]. Mycophenolate has a less suppressive effect on the bone marrow than other cytotoxic agents. However, one still needs to monitor for leukopenia and opportunistic infections. Both azathioprine and mycophenolate have been widely used for solid organ transplants. In that group of patients, both agents were associated with increased rates of infection and tumors [84,85].

Pentoxifylline has been reported as useful in the treatment of acute pulmonary disease [86]. A recent double-blind placebo-controlled trial demonstrated a steroid-sparing effect for the drug [87]. However, dosing is limited by gastrointestinal toxicity. Aprelimate is a new phosphodiesterase 4 inhibitor that is more potent and appears less toxic than pentoxifylline [88]. It has been reported as being effective for sarcoidosis following a small open-label trial of cutaneous disease.

Other agents have been used to treat sarcoidosis. These include thalidomide for chronic cutaneous disease [89,90]. The major limitation of this drug is its association with somnolence, constipation and peripheral neuropathy [89]. Rituximab has also been reported as useful in case reports of refractory sarcoidosis [91,92]. The drug is associated with a risk for reaction to the agent, as well as increased risk for infections, especially viral infections, such as HBV [93].

Expert commentary

Treatment of sarcoidosis depends on the level of symptoms and the duration of disease. Based on current evidence, a specific plan for therapy can usually be developed. While there is no single therapy for all patients, a stepwise approach seems reasonable for most cases.

Five-year view

It should be noted that not all patients respond to therapy. In recent reports, it was found that the mortality from sarcoidosis has remained the same [94] or has risen [95] over the past 20 years, despite the increasing use of anti-inflammatory

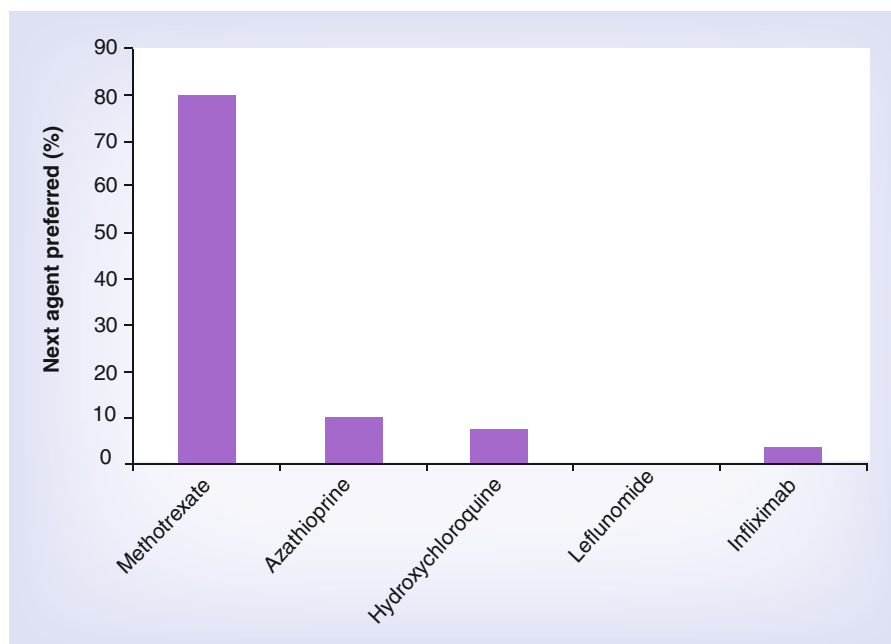


Figure 4. Results of a Delphi analysis. Shows which agent is preferred as the next agent chosen to add to, or replace, corticosteroids for sarcoidosis patients experiencing an inadequate response with corticosteroid use. Data taken from [41].

drugs. There is some controversy about whether the mortality associated with sarcoidosis is as high as the 5% noted in referral centers [96], or the less than 1% noted at primary centers [97]. However, it is clear that there is a subset of severe chronic patients. The rate of these chronic patients appears to be similar at sarcoidosis clinics around the world [98].

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Box 1. Indications for use of anti-TNF monoclonal antibody therapy.

Pulmonary disease with:

- Forced vital capacity less than 70%
 - Level 2 [69,70]
- Disease present for more than 1 year
 - Level 2 [69]
- Elevated C-reactive protein
 - Level 2 [105]

Lupus pernio skin lesions

- Level 2 [16,69]

Refractory neurologic disease

- Level 3 [72,73]

Key issues

- Not all patients with sarcoidosis require therapy.
- Corticosteroids are the drug of choice for initial therapy in most patients.
- Methotrexate and other cytotoxic agents are useful steroid-sparing agents for chronic disease.
- Monoclonal antibodies to TNF have proved useful in treating refractory patients.

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