Postgraduate Course
ERS Copenhagen 2005

Therapeutic options for sarcoidosis: old and new

R.P. Baughman

R.P. Baughman
University of Cincinnati Medical Center
Holmes, Room 1001
Eden Avenue
Albert Sabin Way
45267-0565 Cincinnati
OH
USA
Fax: 1 5135845110
E-mail: bob.baughman@uc.edu

Educational aims

❭ To discuss the role of corticosteroids in treating sarcoidosis.
❭ To provide information about when to consider cytotoxic drugs for chronic sarcoidosis.
❭ To outline how to monitor the use of cytotoxic drugs.
❭ To better understand the differences in response when using anti-tumour necrosis factor agents in treating sarcoidosis

Summary

The decision to treat a patient with sarcoidosis is dependent on many factors, the most important being whether the patient is symptomatic. Initial systemic therapy for symptomatic sarcoidosis usually includes corticosteroids. However, most symptomatic patients will require months to years of therapy. Therefore, alternatives to corticosteroids have been studied. This review will give a brief overview of the effect of corticosteroids and alternative treatments options available.

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The focus of this review will be on sarcoidosis and its treatment; however, much of this information can be applied to other granulomatous diseases. For example, some of the treatment strategies that have been developed for sarcoidosis have also been used for hypersensitivity pneumonitis.

The recommended treatments for sarcoidosis differ from none to a combination of cytotoxic agents. A major reason for this wide spectrum of treatment relates to the variation in disease outcome. Moreover, treatment options vary because no treatment can cure the disease, but rather just control the symptoms. Finally, the preference of the patient and treating physician have an influence. All of these reasons impact on any decisions regarding drug usage and duration of therapy.

Sarcoidosis and corticosteroids

Over the past 10 years, therapy for sarcoidosis has evolved and corticosteroids are no longer the only available treatment option.

Early literature suggested that corticosteroids were effective for sarcoidosis, but the results from these published clinical trials were limited, as placebo could not be used for the most ill patients for obvious ethical reasons. Subsequently, it has been shown that the use of systemic coricosteroid therapy is linked to chronic sarcoidosis.

The first question that should be considered is whether corticosteroids are helpful in sarcoidosis. In the 1950s, several small anecdotal trials revealed beneficial effects of these drugs in sarcoidosis patients who were dying from their disease. In 2002, a meta-analysis on the use of corticosteroids in sarcoidosis patients clearly demonstrated an improvement on chest radiography as compared with the use of placebo [1]. However, despite improvement on chest radiography, corticosteroid use may not improve patient health (see Case summary).

The study by PARAMOTHAYAN and JONES [1] also studied diffusing capacity of the lungs for carbon monoxide ($D_{L,CO}$), although only two trials met their criteria for viable double-blind randomised trials. Overall, corticosteroid therapy was favoured over placebo for $D_{L,CO}$. However, these authors felt that there was not enough evidence to support an improvement in forced vital capacity.

The study by GIBSON et al. [2] is an excellent example of a clinical trial for sarcoidosis patients, since it provides full detail of what actually happened to the patients studied. Out of 150 patients who were observed for 6 months, 33 experienced a deterioration in their health requiring clinical treatment, and 58 got better without the need for any form of therapy (although their chest radiography remained abnormal) and they were not randomised into the trial.

Patients were randomised to selective therapy or were immediately prescribed steroids. If they started to deteriorate after 6 months of observation they were tested. Six out of 31 patients actually deteriorated and were placed on steroids. Patients were treated for 18 months and, on follow-up 5 years later, there was a significant improvement in the vital capacity and a difference in the dyspnoea score. However, it should be noted that an element of bias was introduced into the study as the sickest patients in the placebo group were also treated.

The same effect was also seen in a study examining budesonide [3], where a large number of stage 1, 2 and 3 patients were treated. The most important results were found in patients with stage 2 and 3 disease, i.e. those with pulmonary infiltrates. After 18 months (comprising 3 months of prednisolone and 15 months of budesonide), there was a significant improvement in the steroid group, but no change in the placebo group, which persisted at the 5-year follow-up. It could be argued that this is the best data to support treating patients with 3 months of systemic steroids, followed by 15 months of inhaled steroids. The data look even more impressive when the $D_{L,CO}$ is considered.

Case summary

A patient who had been referred to the current author reported weight gain as a result of taking corticosteroids. The patient had initially been prescribed 20 mg prednisone q.d. (figure 1) but when the dose was reduced to 10 mg q.d. (figure 2) due to the side-effects, the patient's condition deteriorated. This was evident from chest computed tomography, which revealed an increase of infiltrates in various parts of the lung. However, the patient was asymptomatic, with the exception of weight gain and diabetes. Subsequently, the patient was tapered off steroids, has not been taking steroids for 2 years and has had no clinical relapse. Even with abnormal chest radiography, the medical team are quite comfortable monitoring the patient, since his vital capacity has always been >85%. Thus, the decision to give corticosteroid therapy should not be purely based on the results of chest radiography.

Indications for corticosteroid therapy

The American Thoracic Society/World Association for Sarcoidosis and Other Granulomatous Disorders/European Respiratory Society statement [4] has considered the absolute indications for corticosteroid therapy. These indications are presented in table 1.

Utility of corticosteroids

Patients with pulmonary radiographic stage 1 disease, with or without erythema nodosum, and with normal lung function do not require treatment with corticosteroids (grade A recommendation).
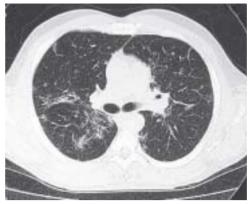
Symptomatic patients with stage 2–3 pulmonary lesions and an impaired lung function respond to treatment with oral corticosteroids (grade A). Patients with newly detected disease respond better than patients who have had sarcoidosis for >2 years (grade A). It is unknown for how long treatment has to be continued and what markers should be used in the decision making for tapering the dose during treatment and when to stop treatment.

Inhaled corticosteroids have been recommended for treating symptoms such as cough, patients with airway obstruction and bronchial hyperresponsiveness; however, this has never been supported by any clinical trials and, thus, is a grade D recommendation.

Conversely, it has been shown that after induction with oral prednisone, using inhaled budesonide is an alternative for treating a patient with sarcoidosis, which is a grade B recommendation. It is important to realise that this

Figure 1
Chest radiograph of patient who was initially prescribed 20 mg prednisone.

Figure 2
Chest radiograph of patient when the dose was reduced to 10 mg.

benefit has only been demonstrated with budesonide.

Another concern is how much to prescribe when there no dose response is observed. Recommendations have ranged 30–40 mg, but this is a grade U recommendation, meaning that there has been no consensus about the starting dose.

Extrapulmonary disease is also a difficult area, since there are no sufficient data to support the use of corticosteroids, although they are commonly used. Hence, it is recommended that the patients should have organ failure or some of the other absolute indications, but this is a grade D recommendation.

Timing of corticosteroid treatment

For a long time, there has been the philosophy that therapy once initiated should not be stopped, especially in patients with a diagnosis of >2 years [5]. However, it is now clear that there are a group of patients who are not necessarily going to relapse, although it is still unclear how to identify these patients.

In a study conducted in Philadelphia, GOTTLIEB *et al*. [6] examined a mostly African-American population. Although there was no

Table 1	Indications for corticosteroid therapy	
Absolute	**Relative**
Neurological	Symptomatic pulmonary
Cardiac	disease
Hypercalcaemia	Arthritis
Ocular	Hepatic
(when topical therapy	SIRS
has failed)	
Other life- or organ-	
threatening disease	

SIRS: systemic inflammatory response system.

specific protocol, patients were treated in a standardised fashion. When therapy was discontinued, patients were followed-up for at least 2 years. The frequency with which steroids were used was recorded and also whether the patients relapsed. From the initial 340 patients, one third did not require therapy in the first 6 months. Interestingly, only nine out of the 118 actually needed therapy in the long term. If patients felt they needed therapy initially, they were treated for 2 years. Half of the patients continued to receive therapy, and therapy was ceased for the remainder, although three-quarters of these patients relapsed.

ACCESS (A Case Controlled Etiologic Study of Sarcoidosis) was a USA-based study, which provided information from 10 centres across the USA on new-onset sarcoidosis patients who were diagnosed within 6 months [7]. Patients were in two general categories: either on no therapy in the first 6 months or on initial therapy. Patients who received initial therapy were still on therapy 2 years later. If they were not on initial therapy, the majority of patients were never treated. There were some patients who were treated and then medication was withdrawn, and there was a small number of patients who were still on therapy 2 years later who were not treated in the first 6 months. After examining the evidence for neurological and cardiac disease, and considering pulmonary function test results, sex, race and age, the significant factor was found to be whether patients were initially prescribed systemic therapy.

Alternative treatments

For patients with chronic disease, alternative treatment to corticosteroids can be categorised into the following three areas: antimicrobials, cytotoxic agents and cytokine modulators (table 2).

Table 2	Categories of alternatives to corticosteroids
Antimicrobials	
	Chloroquine
	Hydroxychloroquine
	Minocycline
Cytotoxic agents	
	Methotrexate
	Leflunamide
	Azathioprine
	Cyclophosphamide
Cytokine modulators	
	Thalidomide
	Infliximab
	Adalimumab
	Etanercept

Antimicrobials

In the literature, there is almost as much data regarding antimalarials as there is for predisone for the treatment for sarcoidosis. The response rate to antimalarials is much greater in cutaneous disease as compared with pulmonary disease.

The use of chloroquine has been effective for some forms of sarcoidosis, mostly skin (grade B). Hydroxychloroquine, which is less toxic, may also be effective, but this is a grade C recommendation since this has not yet been demonstrated in sarcoidosis. Patients who have been prescribed these drugs require a routine eye examination while on therapy (grade D). Minocycline has been reported as helpful for cutaneous sarcoidosis.

Cytotoxic agents

Methotrexate is used in the treatment of rheumatoid arthritis, and has always been effective in lowering the dosage of corticosteroids. As a result, a possible role in sarcoidosis treatment was proposed, despite evidence of dose-dependent toxicity in the liver and, occasionally, the lungs.

In patients treated with methotrexate for >2 years, a high response rate has been achieved for the skin and lungs [8]. Looking at other organs, *i.e.* for neurological and eye disease, a relatively high response rate has again been observed. For patients with neurological disease, non-responders are usually treated with cyclophosphamide. For patients with eye disease, non-responders are treated with a combination of cytotoxic drugs.

When prescribing methotrexate, initial and follow-up laboratory data should be obtained, including information on hepatic and renal function. The inital dose is recommended as 10 mg per week, with a maximum dose of 15–20 mg per week. To reduce toxicity, the dose should be split over the days leaving a rest period, and folic acid should be taken (1 mg per day). The dose should be reduced for neutropenic patients.

Leflunomide is another immunomodulatory agent that is similar to methotrexate. It utilises a slightly different pathway, but it is basically an inhibitor, which must be considered when using either drug. In a recent study [9], it was shown that ~80% of patients had a complete or partial response with the use of leflunomide. Furthermore, it was shown that patients with ocular disease who were treated with a combination of methotrexate and leflunomide had a greater response than with a single cytotoxic drug alone.

Azathioprine also appears to be effective as a steroid-sparing agent in some cases (grade B).

Cyclophosphamide has been shown to be useful in some refractory cases of neurosarcoidosis,

but has been associated with bladder toxicity and, thus, urine analysis should be performed at least once a month for patients who are prescribed this drug (grade B).

Cytokine modulators

Over the past few years, the most frequently discussed cytokine modulators have been thalidomide and infliximab.

Thalidomide is a drug with significant anti-inflammatory properties and has mostly been used in the treatment of *Mycobacterium tuberculosis* and leprosy. It inhibits tumour necrosis factor (TNF) release by alveolar macrophages. However, there are significant side-effects, including toxicity, teratogenesis, somnolence and peripheral neuropathy.

Thalidomide was used as a treatment for patients with lupus pernio, since this is a chronic form of sarcoidosis with a minimal chance of spontaneous remission, and skin lesions are easier to evaluate [10]. A total of 15 patients were studied and the greatest response was seen at a dose of 100 mg. Unfortunately, however, thalidomide was not as effective on other organs.

The use of thalidomide supports the concept that TNF may be an important mediator. It is not yet clear whether thalidomide works by blocking TNF. However, it has raised questions about other agents that specifically block TNF, such as etanercept, infliximab and adalimab. Etanercept is a TNF receptor antagonist, is given subcutaneously and has been shown to be effective in rheumatoid arthritis but not effective in Crohn's disease. Infliximab is a chimeric monoclonal antibody given intravenously, which has been used for both rheumatoid arthritis and Crohn's disease. Adalimumab is a humanised monoclonal antibody that is similar to infliximab, and, given subcutaneously, it has been shown to be equally effective. All three of these drugs work to about the same rate in rheumatoid arthritis. However, there are only limited data showing a benefit in Crohn's disease for anything but infliximab.

Etanercept was not found to be useful in pulmonary sarcoidosis. In an open-label trial of 17 patients with stage 2/3 disease, the study had to be terminated early due to treatment failures [11]. In a subsequent double-blind trial [12], ocular sarcoidosis patients who failed to respond to at least 6 months of methotrexate were randomised to receive either etanercept or saline, after having initial (and follow-up) visits by an ophthalmologist. There was no change in methotrexate dosage during the study, and the ophthalmologist was allowed to adjust the topical therapy frequency and was given the option of providing periocular injections of steroids. The results showed there were essentially no differences between the etanercept and placebo group.

In a retrospective study comparing anti-TNF agents for sarcoidosis, all patients were treated for at least 1 month with either etanercept (n=14), infliximab (n=69) or adalimumab (n=17). The greatest response rate (85%) was achieved with infliximab, whereas rates of ~30% were found with the other two drugs.

In a recent case series [13], 10 patients were treated with infliximab. Nine out of the 10 responded, with six experiencing improvement in skin rash and one each with neurological, liver and muscle manifestations. One patient who had back pain with direct bone involvement did not respond, although the bone lesion improved on magnetic resonance imaging.

Anti-TNF therapy has significant toxicity. The first problem is with regards to allergic reactions, as anaphylaxis can occur rarely in patients who have been prescribed infliximab. As a result, patients should be carefully observed during infusion. There is also an increased risk for infection, and infliximab has a high risk for reactivation of TB. Additionally, anti-TNF therapy increases the risk of mortality in patients who already have advanced stage 3/4 congestive heart failure. Concerns about an increased risk of malignancy are still undecided due to the lack of supportive data.

Others

Tetracyclines benefit some forms of cutaneous sarcoidosis (grade D). Cyclosporin has no apparent effect on pulmonary sarcoidosis, but has reported useful in neurosarcoidosis. There is incomplete evidence to comment on the role for other agents, such as pentoxifylline or formic acid esters.

Radiation may be useful for patients with small, refractory lesions, but is not an effective therapy for larger lesions (grade D).

Conclusions

The therapy for sarcoidosis has become a matter of choosing the best agent for each patient. Therapeutic protocols are increasingly composed of multiple agents, rather than relying on a single drug. The clinician now has multiple agents with which to treat the patient.

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Therapeutic options and management of pulmonary fibrosis: old and new

The Royal Brompton Hospital on its opening in 1846.

R.M. du Bois

R.M. du Bois
Royal Brompton Hospital
Sydney Street
SW3 6NP
London
UK
Fax: 44 2073518336
E-mail: r.dubois@rbht.nhs.uk

Idiopathic pulmonary fibrosis (IPF), with the histological correlate of usual interstitial pneumonia, has an almost uniformly poor prognosis when compared with other idiopathic interstitial pneumonias. To date, therapeutic attempts, including corticosteroids and immunosuppressive agents, have focused on targeting the inflammatory component of the disease with limited success; only 10% of patients derive significant physiological benefit with this approach. Systematic evaluation of different therapeutic regimens has previously been hampered by a non-standardised approach to trial design, diagnostic criteria and treatment protocols. The pathogenesis of IPF has been classically described as a predominantly inflammatory process, in response to an environmental trigger in a genetically susceptible individual, with subsequent fibrogenesis. The relative lack of efficacy of anti-inflammatory therapy has prompted an evolution in the understanding of pathogenesis, focusing on epithelial injury, dysregulation of wound healing and fibrogenesis.

In light of the changing theories concerning the pathogenesis of IPF, the evidence supporting traditional anti-inflammatory therapy, the idiosyncrasies of past study design and the need for standardised treatment guidelines, the emergence of reports of novel therapeutic approaches has been welcome. Recent therapeutic approaches include anti-fibrogenic agents, such as interferon-γ, pirfenidone and bosentan, and anti-oxidant therapies, such as

N-acetylcysteine, whereas many others are in the preliminary stages of laboratory and clinical evaluation. At present, the course of IPF remains relentlessly progressive for most patients. The development of new therapeutic approaches, recruitment into well-constructed large multicentre trials, and ongoing laboratory and clinical research brings renewed enthusiasm to this devastating disease.

Current practice

Current practice at the Royal Brompton Hospital Interstitial Lung Disease Unit (London, UK) is to initiate treatment at the preliminary identification of functional or physiological compromise, or after a documented decline in lung function parameters if they were close to normal at the first visit.

First-line therapy includes low-dose corticosteroid (prednisolone 10 mg daily or 20 mg on alternate days) and azathioprine (initially 50 mg daily and subsequently increased after 4 weeks to 2.5 mg·kg⁻¹·day⁻¹ (maximum 200 mg) if well tolerated and no evidence of bone marrow suppression or hepatotoxicity on weekly blood tests). If tolerated, therapy should continue for a minimum of 6–12 months to allow time to demonstrate efficacy, and treatment is continued for 24 months in the first instance if evidence of physiological improvement, stability or slowing of decline is documented. Decisions on longer-term therapy are made individually. In the event of an accelerated phase (akin to subacute diffuse alveolar damage, resulting in a step down in gas exchange), where infection, fluid overload and pulmonary embolic disease have been excluded, high-dose corticosteroid therapy can be considered; 500–1,000 mg of intravenous methylprednisolone on 3 consecutive days followed by objective assessment of response is the strategy followed at the Royal Brompton Hospital Interstitial Lung Disease Unit but there is no evidence base for this. Under these circumstances, a single infusion of cyclophosphamide at 600 mg·m⁻² is also considered when deterioration is marked, but, again, there are no data to support this regimen.

The current author's therapeutic approach to non-specific interstitial pneumonia mirrors the IPF regimen; however, if evidence of physiological decline and ⁄ or significant ground-glass attenuation is found, a lower threshold for intravenous high-dose corticosteroid therapy is employed as outlined above. The use of nocturnal and portable supplemental oxygen should

be considered in order to reduce right heart strain and increase exercise capacity. Lastly, if symptomatic and lung function decline are documented despite optimal medical management, patients should be assessed for their suitability for lung transplantation. In general, patients with IPF should be referred for transplant assessment when the gas transfer drops below 35–40% predicted if decline is gradual but earlier if the pace of change is more rapid. Late referral has been identified as a major determinant of death on transplant waiting lists.

Novel therapies

The place for novel therapies has yet to be identified. Encouraging signs have emerged from recently published studies, including *post hoc* secondary analyses in an interferon-γ study and also a pirfenidone multicentre study from Japan. Further phase 3 studies are either underway or planned. The publication of the *N*-acetylcysteine study together with awaited analyses of etanercept and bosentan will emerge at the logical approach but trials of such combinations will hopefully provide further encouragement. It is likely that future approaches will adopt the cancer model of comparing current "best treatment" with novel approaches. It is likely that a combination of anti-oxidant, anti-inflammatory and anti-fibrotic agents will emerge at the logical approach, but trials of such combinations will cause consternation regarding drug interaction, but this concept will have to be grasped sooner rather than later.

Conclusion

In summary, international consensus on the management of IPF has underscored the marginal benefit of existing therapies, since, for most patients, IPF remains a progressive and irreversible disease. New insights into pathogenesis have suggested a model of sequential acute lung injury and incremental fibrosis, which concurs with the clinical course of IPF: a picture of stepwise progression, recurrent episodes of clinical deterioration, and intercurrent acute exacerbations. Major advances in survival will inevitably rely on the development of novel agents, and promising data have raised the profile of anti-fibrogenic and antioxidant therapies, in addition to conventional anti-inflammatory approaches. At present, the prognosis of IPF is not dissimilar to many malignancies, and should prompt clinicians to consider all patients for entry into well-designed drug trials, taking heed of historical study pitfalls.

Suggested further reading

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