CHAPTER 20

Therapy for sarcoidosis

R.P. Baughman, E.E. Lower

University of Cincinnati Medical Center, Cincinnati, OH, USA.

Correspondence: R.P. Baughman, 1001 Holmes Eden Ave, Cincinnati, OH 45267-0565, USA. Fax: 1 5135585110; E-mail: bob.baughman@uc.edu

The recommended treatments for sarcoidosis differ from none to a combination of cytotoxic agents [1]. A major reason for this wide spectrum of treatment relates to the variation in disease outcome. Moreover, treatment options vary because no treatment cures the disease, but is rather a means of controlling symptoms. Finally, there is the preference of the patient and treating physician. All of these reasons impact on the decision regarding drug usage and duration of therapy.

The approach to therapy in sarcoidosis revolves around several important issues. These are summarised in table 1.

One issue concerns the symptoms a patient is suffering from. In most series, at least a third of sarcoidosis patients are asymptomatic and, therefore, never require treatment for symptoms [2–4]. In one study, a third of patients with parenchymal involvement on chest radiography experienced chest radiographic improvement over a 6-month observation period [5]. This group had benign disease, with only 20% of the patients considered sick enough to require systemic therapy on presentation. The highest recorded proportion of patients requiring systemic therapy on presentation is 67%. This was from a clinic of mostly African-American patients [6].

For the asymptomatic patient with persistent parenchymal infiltrates, two studies have suggested that therapy changes the natural history of the disease. In one study, patients were treated with 18 months of continuous systemic therapy *versus* systemic therapy only if needed. In the latter group, six out of 31 (19%) received corticosteroid therapy. Despite the fact that not all patients in the control group received no therapy, the control patients overall exhibited a persistently lower Vital Capacity (VC) and higher level of dyspnoea 5 yrs after the discontinuation of any therapy [5]. In a study comparing a regimen of 3 months of systemic corticosteroids followed by 15 months of inhaled steroids (budesonide) *versus* placebo, PIETINALHO *et al.* [7] reported that corticosteroid treatment was associated with a significantly higher carbon monoxide diffusing capacity of the lung and better chest radiographic pattern than in placebo patients at the end of treatment. An additional analysis 5 yrs after completion of therapy found persistent benefit of corticosteroid therapy for 18 months in patients with parenchymal infiltrates at the time of treatment [8]. Interestingly, the authors also reported that patients treated with placebo experience a higher rate of deterioration requiring systemic therapy during the 5-yr observation period.

Table 1. – Questions to be answered in deciding on therapy for sarcoidosis

Is the patient symptomatic?
Can the symptoms be controlled with topical therapy?
Does the patient exhibit life- or organ-threatening disease?
Is the patient experiencing, or is likely to experience, chronic disease?
Does the patient have a relative or absolute contraindication to any specific therapy?

Eur Respir Mon, 2005, 32, 301–315. Printed in UK - all rights reserved. Copyright ERS Journals Ltd 2005; European Respiratory Monograph; ISSN 1025-448x. ISBN 1-904097-22-7.

The success of budesonide in the study of PIETINALHO *et al.* [8] raises the question as to whether sarcoidosis patients can be controlled using inhaled therapy alone. Although the use of inhaled budesonide was more efficacious than placebo in some studies [9, 10], others have not found budesonide useful in controlling pulmonary disease [11]. Fluticasone has not been found useful in treating either acute or chronic symptomatic disease [12, 13]. However, these drugs may still be useful in controlling cough, if that is the major problem [12].

Topical therapy appears more successful for controlling skin lesions and anterior uveitis. Corticosteroids, in various preparations, have been used since the mid-1990s [14]. Tacrolimus has recently been reported as a beneficial topical therapy for refractory cutaneous disease [15]. Ocular disease has been treated with topical drops and periocular injections of corticosteroids [16]. However, local therapy can lead to complications, such as glaucoma and cataract formation [17]. There is also a report that topical ocular corticosteroid therapy delays the resolution of pulmonary sarcoidosis [18].

The use of systemic therapy for sarcoidosis is usually driven by symptoms. An absolute requirement for systemic therapy includes manifestations which are life- or organ-threatening. In long-term studies analysing mortality due to sarcoidosis, the most common causes of death are pulmonary, cardiac, neurological and hepatic [19–21]. Table 2 lists the mortality reported in a cohort of patients followed at a specialised clinic, and focuses on the relative frequency of death caused by pulmonary, neurological and cardiac disease [19]. For pulmonary disease, a low VC is a relative indicator of increased mortality. The treatment of respiratory disease may improve survival. For example, three out of nine patients showing a lowest VC of <1 L died due to respiratory failure. Only one out of six patients whose VC increased with therapy to >1 L died; however, two out of four patients without improvement in their VC died during the 7-yr observation period [19]. Subsequent studies performed on patients with respiratory failure awaiting lung transplantation suggest that the presence of pulmonary hypertension is associated with increased mortality. An elevated right atrial pressure was associated with the worst prognosis [22–24].

In an attempt to identify prognostic markers of chronic disease, several studies have noted certain markers that are associated with resolution of disease, and others that are associated with a prolonged disease state. The landmark study of NEVILLE *et al.* [25] of 818 patients is summarised in figure 1. In addition, renal calculi are another marker of chronic disease [26].

One biological marker of chronic disease has been increased neutrophil and eosinophil numbers in bronchoalveolar lavage (BAL) fluid [27]. The increased neutrophil numbers are associated with increased interleukin-8 levels in the BAL fluid [28]. Recent studies have confirmed the importance of this finding [29, 30].

Regardless of presentation, the clinical outcome of the patient is best determined with time. Although figure 1 illustrates that patients with erythema nodosum and stage 1 chest radiographs usually experience disease resolution within 2 yrs, a subgroup of patients

Table 2. – Mortality in a cohort of patients with sarcoidosis followed for 7 yrs

Organ involvement	Cases n	Deaths n (%)
Any	479	22 (4.6)
Lung		
Vital capacity >1.5 L	438	3 (0.68)
Vital capacity <1.5 L	41	10 (24)
Cardiac	20	3 (15)
Neurological	54	4 (7.4)

Data taken from [19].

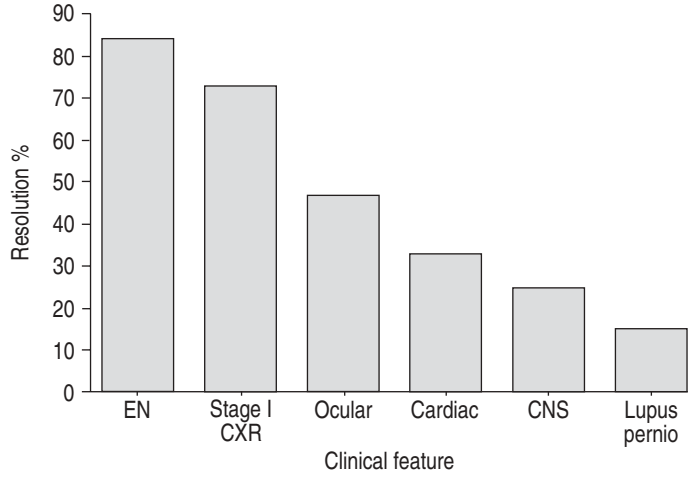

Fig. 1. – Frequency of resolution of chest radiograph (CXR) after 2 yrs in sarcoidosis patients presenting with various clinical features. EN: erythema nodosum; CNS: central nervous system. Adapted from [25].

exists with even this benign presentation who require long-term therapy [31]. In a recent worldwide survey of sarcoidosis clinics, >50% of patients followed for >5 yrs after diagnosis still required therapy. This includes 10% of patients experiencing disease relapse requiring increased systemic therapy in the previous year. Figure 2 indicates that there was no major geographical difference in the incidence of chronic disease between the five centres [31].

Relative and absolute contraindications exist for all drug therapies. In sarcoidosis,

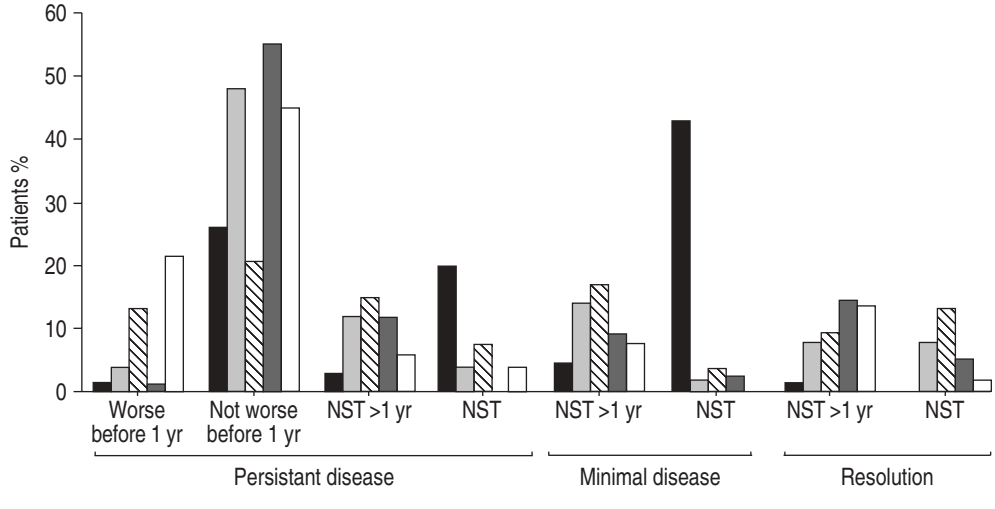

Fig. 2. – Percentage of patients (n=50) from each multinational site (■: Kyoto, Japan; ▩: Milan, Italy; ▧: Maastricht, The Netherlands; ▩: Charleston, NC, USA; □: Cincinnati, OH, USA) in each general category ≥5 yrs after diagnosis. Patients could show resolution (no evidence of disease) or minimal (<10% of maximal disease) or persistent (>10% of maximal disease) disease, and could have never been given systemic therapy (NST), none in the previous year (NST >1 yr) or received therapy in the past year. Patients with persistent disease may also have worsened in the past year. Data taken from [32].

patients who have received corticosteroids are often anxious to find alternatives. As more treatment options become available for sarcoidosis, the clinician can avoid toxicity. However, the perfect drug for sarcoidosis is yet to be found.

In an era of rising health costs, clinicians need to consider the potential cost of various agents. Corticosteroids are very inexpensive, whereas some of the newer agents, such as infliximab, are relatively expensive.

Individual agents

Corticosteroids

Corticosteroids remain the standard agent to which all other drugs are compared (table 3). Introduced in the 1950s for sarcoidosis [33], these drugs were quickly shown to be effective in treating the disease [34]. The early reports of the success of corticosteroids in treating sarcoidosis were followed by a series of negative studies when the drug was compared to placebo in randomised trials [35, 36]. Other groups found the drug quite useful in the management of chronic pulmonary disease [37, 38].

A meta-analysis of corticosteroid therapy for sarcoidosis confirmed the value of this treatment [39]. However, this meta-analysis also highlights some of the problems of prior clinical trials, including the exclusion of symptomatic patients (who were all treated) and the relatively short follow-up. When corticosteroids were administered for >6 months, drug therapy was significantly better than placebo [40].

The most controversial area of corticosteroid therapy is the asymptomatic individual with persistent infiltrates. As noted above, there are two trials demonstrating benefit for patients with persistent infiltrates even if they show no symptoms. Two regimens have been studied: systemic corticosteroids for 18 months [5], and 3 months of systemic corticosteroids followed by 15 months of high-dose inhaled budesonide [8]. However, the

Table 3. – Drug therapy for sarcoidosis

Class	Drug	Dose	Comments
Corticosteroids	Prednisone	5–40 mg	Initial dose higher; reduce to minimal, tolerable and effective dose
	Prednisolone	5–40 mg	
	Budesonide	800–1600 μg	Inhaled therapy
	Triamcinolone		Used in topical therapy for skin
Cytotoxic	Methotrexate	5–15 mg weekly	Takes up to 6 months to be effective
	Azathioprine	50–250 mg daily	More leukopenic than methotrexate
	Chlorambucil	2–12 mg daily	Higher rate of malignancy than other agents
	Leflunomide	10–20 mg daily	Similar to methotrexate, but less nausea
	Cyclophosphamide	50–150 mg orally daily or 500–2000 mg *i.v.* every 2 weeks	Higher rate of side-effects, but associated with higher response rate than other cytotoxic agents
Antimicrobial agents	Chloroquine		
	Hydroxychloroquine	200–400 mg daily	Less ocular toxicity than chloroquine
	Minocycline	100–200 mg daily	Rarely associated with immune toxicity
Cytokine modulation	Pentoxifylline	200–400 mg up to 3 times·day^{-1}	High doses may be needed to block TNF
	Thalidomide	50–200 mg daily	Teratogenic, a potential major concern
	Infliximab	5 mg·kg^{-1} *i.v.* every 4–8 weeks after loading doses	Increased rate of infection and allergic reaction

TNF: tumour necrosis factor.

amount of improvement demonstrated at the end of treatment and 5 yrs later does not appear to be clinically significant. In addition, there is concern that the institution of corticosteroid therapy may increase the likelihood of development of chronic disease [6], although this was not seen in the two controlled trials [5, 8]. Following these studies, one recommendation is that asymptomatic patients with persistent disease should not be treated with corticosteroids [1].

The initial and maintenance dose of corticosteroids varies from centre to centre. It appears that the dose used to place a patient in remission is higher than that needed to maintain the remission. As summarised in figure 3, JUDSON [41] described the six phases of corticosteroid therapy for sarcoidosis. The duration of therapy in each stage varies between patients and treating physicians. Overall, patients usually receive $\geq$1 yr of therapy.

For pulmonary disease, the recommended initial dose of prednisone (or prednisolone) is 20–40 mg·day^{-1} [1]. The dose is tapered over the next 6 months to <20 mg. Some clinicians prefer to use an alternate-day regimen. A higher initial dose is often used for cardiac or neurological disease.

Corticosteroid therapy is not without toxicity. H. Cushing first described hypercortisolism as a clinical entity. Pharmacological doses of glucocorticoids can lead to hyperglycaemia, hypertension, weight gain, osteoporosis, acne, glaucoma and cataracts. Figure 4 summarises the most common daily toxicities reported by patients treated for pulmonary sarcoidosis for 1 yr. Those receiving prednisone at a dose of >10 mg·day^{-1} reported a significantly higher rate of each complaint [12].

Methotrexate

The antimetabolite methotrexate has become one of the standard agents used for sarcoidosis [1, 42, 43]. Widespread use has developed because of its efficacy against various disease manifestations, including cutaneous lesions [44, 45], pulmonary disease [42, 44], arthritic manifestations [46], ocular disease [16, 46, 47] and neurological disease

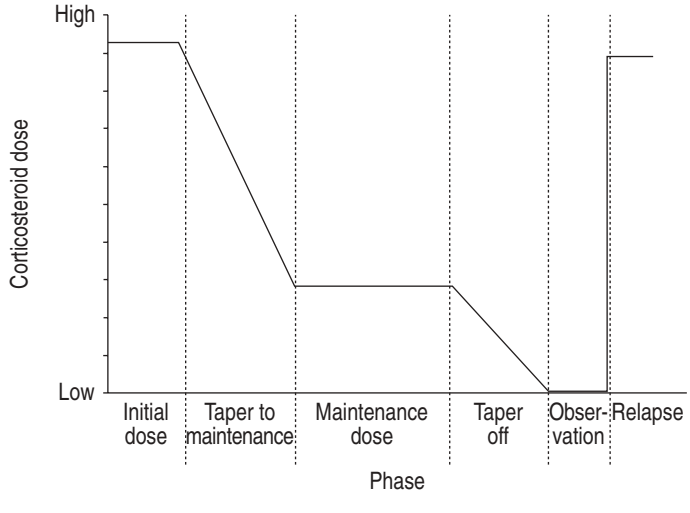

Fig. 3. – The six phases of corticosteroid therapy for patients with sarcoidosis. Although not all patients relapse, with relapse, the dose of treatment required is often as high as that needed to induce the initial remission [41].

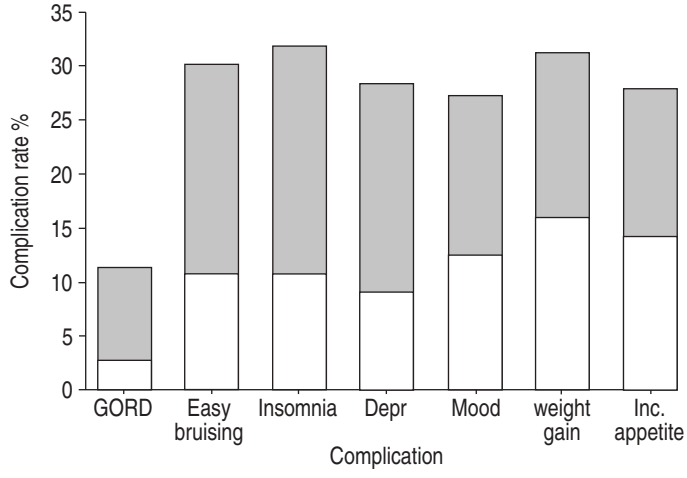

Fig. 4. – Self-reported rate of individual complications (□: always; ■: most of the time) due to systemic corticosteroids during a 1-yr study [12]. GORD: gastro-oesophageal reflux disease; Depr: depression; Mood: moodiness; Inc.: increased.

[48]. In all of these manifestations, methotrexate has been reported as effective in at least two-thirds of patients treated.

The original description of methotrexate usage for sarcoidosis was in 1968 [49]. Owing to concerns regarding hepatotoxicity, the drug was initially used for only brief periods, often <6 months. In a series of patients with refractory disease treated with methotrexate for prolonged periods, it was demonstrated that methotrexate could take up to 6 months to show objective evidence of effectiveness [50]. This delay in effect of methotrexate is also seen with other cytotoxic drugs. With the introduction of the methotrexate protocol using drug for $\geq$6 months before evaluating effectiveness, methotrexate has been widely used for sarcoidosis.

The major toxicities of methotrexate can be divided into acute and chronic. Acute problems include leukopenia, gastrointestinal symptoms and mucosal ulcers. These side-effects are dose-related and can often be minimised by the use of folic acid. For the symptomatic patient or patient receiving >10 mg methotrexate per week, the authors usually prescribe 1 mg folic acid daily [51]. Leucovorin can decrease the side-effects appreciated with high-dose methotrexate. However, this is more expensive and usually not needed at the low doses prescribed for sarcoidosis. Since methotrexate is excreted by the kidneys, patients with significant renal impairment should not receive the drug.

Chronic use of methotrexate can be associated with potential pulmonary toxicity and hepatotoxicity. Although methotrexate pulmonary toxicity seems to be associated with the cumulative dose, it can be seen at any time during therapy [52, 53]. On treating 209 sarcoidosis patients with methotrexate, six were reported to have developed cough that resolved with discontinuation of the drug [54]. Interestingly, patients with methotrexate-associated cough did not experience cough when treated with leflunomide [55]. Hepatotoxicity has long been described with methotrexate. Although official guidelines have been established for performing liver biopsy procedures in rheumatoid arthritis patients undergoing long-term methotrexate therapy [56], no such guidelines have been developed for sarcoidosis patients. One group usually performs liver biopsy procedures after every 1 g cumulative dose of methotrexate. To date, methotrexate-associated toxicity has been seen in liver biopsy specimens, but no clinically significant liver damage has

been identified [57]. Other groups have monitored patients using serum liver function tests only [42].

Azathioprine

This cytotoxic drug has been widely used for other interstitial lung diseases, including pulmonary fibrosis [58]. Azathioprine has been reported useful in pulmonary sarcoidosis [59–61], however not all authors have reported efficacy in treating chronic pulmonary disease [62]. The major limitation of current reports regarding azathioprine is the small number of patients studied. Most series include <15 patients, with the exception of one [54], which reported that 19 out of 35 sarcoidosis patients were either stable or in remission with azathioprine therapy. In addition to pulmonary disease, it has been reported as useful in treating neurological [63] and hepatic disease. Since it has less liver toxicity than methotrexate, it may be a safer drug to use in hepatic impairment. However, severe hepatotoxicity has been reported with azathioprine [64].

The usual oral dose of azathioprine is 2–3 $mg \cdot kg^{-1}$. The major toxicities are leukopenia and gastrointestinal toxicity. In some series, these side-effects have led to discontinuation of the drug in >20% of patients [65]. Polymorphisms of the thiopurine *S*-methyltransferase can predict the pancytopenia from azathioprine, but are not predictive of gastrointestinal toxicity [66].

Other cytotoxic drugs

Other cytotoxic drugs have also been reported as beneficial in sarcoidosis. However, experience with these drugs has been more limited. In some cases, these drugs may have a specific ideal niche.

Leflunomide was developed as an analogue of methotrexate with significantly less toxicity [67, 68]. Pulmonary toxicity is a rare but serious problem with methotrexate. It does not appear to be a problem with leflunomide [55, 68]. Since leflunomide shows less toxicity than methotrexate, it has been used in combination with methotrexate to treat inflammation [69]. A randomised trial showed that these agents were synergistic in the treatment of rheumatoid arthritis [70].

For sarcoidosis patients, leflunomide was reported as effective in 25 out of 32 (78%) patients treated [55]. This included 12 out of 15 (80%) treated with both methotrexate and leflunomide. The drug was well tolerated, with only three (9%) patients discontinuing the drug because of toxicity. All three discontinued the drug because of gastrointestinal toxicity.

Chlorambucil has also been reported as efficacious in eight out of 10 chronic sarcoidosis patients [71]. However, there does not seem to be an additional benefit of chlorambucil over methotrexate or azathioprine. Since chlorambucil is associated with an increased risk of myeloproliferative malignancies, the drug has been used sparingly in sarcoidosis.

Cyclophosphamide has also been used for refractory sarcoidosis, especially neurological disease [48, 72, 73]. It has been reported as successful in patients who have failed other therapies [48, 74]. Cyclophosphamide is a cytotoxic agent clearly associated with increased risk of malignancy. This is especially the case when the drug is given orally as a daily agent. In patients treated for >1 yr on a daily basis, the risk of bladder cancer increases [75]. This risk of cancer appears to be less when the drug is given using an intermittent *i.v.* regimen. Therefore, the recommended regimen for treating neurosarcoidosis is an intermittent *i.v.* regimen [48, 72].

Antimicrobial agents

Since the early 1960s, antimalarial agents have been used to treat sarcoidosis [76, 77]. Since these agents work as anti-inflammatory drugs, they have been used for various rheumatological conditions, such as rheumatoid arthritis and lupus erythematosus.

Benefits of both hydroxychloroquine and chloroquine have been reported in the treatment of cutaneous sarcoidosis [76–78]. This efficacy is, in part, related to the concentration of these drugs in the integument. In addition, these agents are effective in the treatment of hypercalcaemia due to sarcoidosis [79]. The agents also seem effective in selected cases of neurosarcoidosis [80]. The overall effectiveness of antimalarial drugs for sarcoidosis appears to be <50% [54].

Ocular toxicity is a major concern with the use of chloroquine, but appears to be much less frequent with the use of hydroxychloroquine [81]. Gastrointestinal intolerance is dose-limiting in some patients.

Minocycline and doxycycline have also been reported beneficial in treating cutaneous sarcoidosis [82]. In one series of chronic cases, eight out of 12 patients experienced a complete response of their skin lesions. The mechanism of action of these drugs remains unclear. As tetracyclines are bactericidal for *Propionibacterium acnes*, these drugs may work by killing the putative agent of sarcoidosis, *P. acnes* [83]. However, other antibiotics, such as clindamycin, which readily kill *P. acnes*, show no apparent benefit in sarcoidosis. Perhaps minocycline and doxycycline act as anti-inflammatory agents [84, 85], since these drugs have been reported useful in other chronic inflammatory conditions, such as scleroderma [86] and rheumatoid arthritis [87].

Immune modulators

There are several other efficacious agents for the treatment of sarcoidosis. The common mechanism of action of these drugs is their effect on the immune response, especially the suppression of tumour necrosis factor (TNF), a key cytokine in chronic sarcoidosis. Several groups have shown that alveolar macrophages from patients with active sarcoidosis release increased levels of TNF [88–90]. Recent studies have demonstrated that patients with active disease, despite corticosteroid therapy, may still release excessive amounts of TNF [91]. This has led to the introduction of agents with anti-TNF activity [92].

Pentoxifylline suppresses cytokine release by alveolar macrophages [93]. This suppression of release by alveolar macrophages seems to be more effective against TNF than against other cytokines in active sarcoidosis [94]. This drug has been reported as successful in treating acute sarcoidosis [95].

Thalidomide is another agent known to suppress TNF release by alveolar macrophages [96]. This drug has been reported useful in treating cutaneous sarcoidosis [97–99]. However, at the doses useful for treating cutaneous lesions, TNF activity was not suppressed in the cutaneous lesions of sarcoidosis [100]. Since thalidomide has other anti-inflammatory and anti-angiogenic properties [101], its mechanism of action in sarcoidosis remains unclear [100].

Since thalidomide is a teratogenic drug, patients treated with this drug in the USA must participate in a closely supervised drug administration programme. The other toxicities of thalidomide are usually dose-related and include somnolence, constipation, peripheral neuropathy and rash. In a dose escalation study of cutaneous sarcoidosis, 12 out of 14 patients responded to 100 mg thalidomide, whereas all responded to 200 mg [97]. Since patients tolerated the 100 mg dose well, this has become the authors' recommended initial dose of the drug.

With the use of molecular biology, biological agents which block TNF have been developed. These include the TNF receptor antagonist etanercept and the chimeric monoclonal antibody infliximab. These agents are both effective for rheumatoid arthritis [102, 103]. However, infliximab [104], but not etanercept [105], has been found effective in treating Crohn's disease.

Infliximab has been reported beneficial for the treatment of refractory sarcoidosis [106–109]. Various disease manifestations, including cutaneous lesions [106, 108], pulmonary disease [106], ocular disease [108, 110, 111] and neurological disease [107], respond to therapy. A multicentric multinational placebo-controlled trial examining the effectiveness of infliximab for pulmonary sarcoidosis is underway.

Not all TNF blockers are beneficial. Etanercept, a TNF receptor antagonist, has not been found to be effective for most cases of pulmonary sarcoidosis in an open-label clinical trial [112]. In a randomised double-blind trial, etanercept was no more effective than placebo in controlling chronic ocular sarcoidosis [113].

The reason for the apparent differences in response rate between etanercept and infliximab is not entirely clear. One possible explanation is the difference in mechanism of action (a receptor antagonist *versus* an antibody). Another possibility is that infliximab can lead to antibody binding on the surface of cells, releasing TNF. In turn, this can lead to apoptosis induced by infliximab, but not etanercept [114].

Several major toxicities are encountered with the anti-TNF therapies. One of the more serious concerns is the increased risk of tuberculosis and similar infections [115]. The risk seems to be higher for infliximab than for etanercept. In addition, both drugs can lead to allergic reactions. With etanercept, the reaction is usually confined to the subcutaneous injection site. Infliximab, which is delivered *i.v.*, can cause systemic reactions, including anaphylaxis. When both drugs were studied as possible treatment for patients with advanced heart failure, there was a possible increase in mortality for those receiving either anti-TNF therapy [116, 117]. Since follow-up is short, the long-term risk with these drugs remains unclear. An association with non-Hodgkin's lymphoma has been suggested for both etanercept and infliximab [118], but the overall risk still seems to be low and may be related to the underlying disease [119].

Conclusion

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 [120]. The clinician now has multiple agents for treating the patient.

Summary

The decision to treat a patient is dependent on many factors, the most important being whether or not the patient is symptomatic. Initial systemic therapy for symptomatic sarcoidosis usually includes corticosteroids. However, most symptomatic patients require months to years of therapy. Therefore, alternatives to corticosteroids have been studied. These include methotrexate and azathioprine. Of these two cytotoxic drugs, methotrexate has been the more extensively investigated. Both drugs work in the majority of, but not all, patients.

Refractory sarcoidosis patients exist, who show persistent disease despite high doses of corticosteroids. Agents that block tumour necrosis factor (TNF) have been shown to be of benefit in some of these refractory cases. Thalidomide has been useful in refractory skin lesions. Infliximab, a monoclonal antibody directed against TNF has been shown to be helpful in some cases of severe refractory disease. With this array of available agents, the clinician can choose to use either single agents or combinations of agents for treating the individual sarcoidosis patient. The goal of therapy is to minimise symptoms with the lowest risk to the patient.

Keywords: Azathioprine, hydroxychloroquine, infliximab, methotrexate, prednisone.

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