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REVIEW

# Management strategies for pulmonary sarcoidosis



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**Abstract:** Sarcoidosis is a systemic inflammatory condition with an unexplained predilection for the lung: over 90% of patients have radiographic or physiological abnormalities. Respiratory physicians therefore often manage patients, but any organ may be involved, with noncaseating granulomas the characteristic feature. Sarcoidosis is the commonest interstitial lung disease (ILD), differing from most other ILDs in that many patients remain asymptomatic or improve spontaneously. Careful baseline assessment of disease distribution and severity is thus central to initial management. Subsequently, the unpredictable clinical course necessitates regular monitoring. Sarcoidosis occurs worldwide, with a high prevalence in Afro-Caribbeans and those of Swedish or Danish origin. African Americans also tend to have severe disease. Oral corticosteroids have been used since the 1950s, with evidence of short to medium response; more recent studies have examined the role of inhaled steroids. Long-term benefits of steroids remain uncertain. International guidelines published in 1999 represent a consensus view endorsed by North American and European respiratory societies. Updated British guidelines on interstitial lung disease, including sarcoidosis, were published in 2008. This review describes current management strategies for pulmonary disease, including oral and inhaled steroids, commonly used alternative immunosuppressant agents, and lung transplantation. Tumor necrosis factor alpha inhibitors are briefly discussed.

**Keywords:** sarcoidosis, corticosteroids, methotrexate, tumor necrosis factor alpha

## Introduction

Sarcoidosis is the commonest form of interstitial lung disease (ILD). It affects men and women of all races around the world, typically aged 20 to 40. Prevalence varies with geography: reported figures range from 1.33 (in White European populations) to 47 (in African American populations) per 100,000 in North America, and 64 per 100,000 in Scandinavia.[1,2] A registry-based Danish study reported an overall incidence of 7.2 per 100,000 person years.[3] A recent British study concluded that overall incidence rate was 5.0 per 100,000 person-years, being highest in London, the West Midlands and Northern Ireland, and that incidence had remained stable between 1991 and 2003.[4] In addition to having a high prevalence of sarcoidosis, Blacks and Afro-Caribbeans also suffer more severe disease. The cause of sarcoidosis remains unknown, but genetic factors affect susceptibility and prognosis.

## Diagnosis

Multiple organ involvement is typical. The sarcoidosis phenotype differs between populations, but the ACCESS study showed that, in a large North American cohort,

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the most commonly affected organs are the lungs, skin, lymph nodes, eyes and liver.[5] The lungs are involved in over 90% of patients, who are therefore often seen by a respiratory specialist in the first instance. Presentation is highly variable, depending on the pattern of organ involvement and speed of onset, and there is no single specific or sensitive diagnostic test. Diagnosis therefore depends on establishing a consistent clinical picture, noting symptoms, signs and characteristic clinical features such as consistent radiological and physiological abnormalities, excluding other differential diagnoses (in particular tuberculosis and lymphoma), and on demonstrating the presence of noncaseating granulomas in one or more affected organs.

## Radiological appearances

Pulmonary sarcoidosis is traditionally classified by chest radiograph (CXR) appearances, as originally proposed by Scadding. Although increasingly being supplanted by more sensitive and detailed imaging modalities such as high resolution computed tomography (HRCT) scanning, the CXR stages 0–IV have the merit of modest correlation with prognosis (Table 1). Spontaneous resolution occurs in 55% to 90% of patients with stage I disease, 40% to 70% with stage II disease, and 10% to 20% with stage III disease. Fibrosis is not reversible, even with treatment, and may be associated with the development of bronchiectasis and aspergillomas. The CXR is thus an important part of initial evaluation and assists in guiding treatment decisions.

## The inflammatory response

The inflammatory response is characterized by activated macrophages and CD4 helper T lymphocytes, with a pattern of cytokine production most consistent with a Th1-type immune response triggered by antigen. Depressed cutaneous delayed-type hypersensitivity explains the typically negative tuberculin test. T cell receptor (TCR) studies suggest the existence of a population of T cells with restricted TCR usage, suggesting that a specific antigen triggers the disease. It is relevant to novel therapeutic strategies that tumor necrosis factor alpha (TNFα) up-regulates endothelial cell adhesion molecules involved in leukocyte binding, stimulates T lymphocyte release of interferon gamma (IFNγ), and enhances T lymphocyte proliferation. The net result is amplification of the steps involved in antigen recognition, cytokine release, inflammatory cell recruitment and granuloma formation.

**Table 1** Chest radiograph appearances in sarcoidosis

| Stage | Lymph node enlargement | Parenchymal disease |
|---|---|---|
| 0 | No | No |
| I | Yes | No |
| II | Yes | Infiltrates |
| III | No | Infiltrates |
| IV | Yes or No | Fibrosis |

## General management strategies

Clear communication to patients about diagnosis and management is vital, given clinical and scientific uncertainties around the cause of the condition, treatment and prognosis, and the abundance of poor quality and sensationalist information available on the internet. Many North American, European and British professional societies and major charities now provide excellent patient information leaflets which can readily be downloaded from their websites.

Although patients with pulmonary sarcoidosis are less likely to smoke than their peers, the disease is not less severe in smokers[6] and respiratory professionals agree that smoking cessation advice should be offered to all patients. While there are no randomized controlled trials of pulmonary rehabilitation in sarcoidosis, patients with pulmonary fibrosis causing deconditioning, disabling breathlessness, impaired quality of life, nutritional deficits, fatigue and social isolation share many features in common with those suffering from chronic obstructive pulmonary disease (COPD), and should be considered for pulmonary rehabilitation. Sarcoidosis patients with pulmonary fibrosis who fulfil criteria for supplemental oxygen, whether ambulatory or long-term, should be assessed and managed according to national guidelines. Palliative care may be appropriate in a minority of patients when all other forms of treatment have been exhausted.

## Treatment with oral corticosteroids

There are no clear criteria for initiating corticosteroid therapy for pulmonary disease. Spontaneous remission occurs in up to 90% of patients; the natural history is variable; the long-term effects of treatment remain unclear; and there are important potential adverse effects of steroid treatment.[7,8] However, the value of oral corticosteroids in pulmonary sarcoidosis was first reported in the 1950s,[9] and they have been widely used since the 1960s. An early study in a small series showed that a short course of adrenocorticotrophin hormone (ACTH) or cortisone attenuated infiltrates seen on CXR, and that prolonged cortisone treatment led to remission of granulomas in repeat biopsy samples.[10] Both uncontrolled and controlled studies have confirmed clinicians' observations of short to

medium term (weeks to months) symptomatic, radiographic and functional improvement. Even in patients with chronic disease previously untreated for several years, oral steroids can have short-term clinical value.[11]

The long-term benefits of oral steroid treatment, in particular whether they prevent pulmonary fibrosis and/or improve survival, remain unclear,[12] with most studies showing no clear advantage. The numbers of patients in such studies ranges from 17 to 172, and interpretation is complex because of differences in disease phenotype, with some patients showing spontaneous regression and varying degrees of residual scarring, while others develop persistent disease. Significant long-term disability caused by pulmonary fibrosis is estimated to arise in 3% to 20%.[13]

Inclusion in these studies of patients with stage I disease on CXR is contentious because of the high rate of spontaneous resolution in this group. In most series steroids were started when patients presented, whereas in reality most respiratory specialists delay treatment in favor of careful monitoring. Most studies used a treatment protocol which did not include gradual tapering of the dose according to response, although this is also common clinical practice. Ethnic variation is another important consideration: most North American studies included a large proportion of black and Afro-Caribbean patients in whom sarcoidosis is often more severe. Their results may therefore not be applicable to European populations.

The British Thoracic Society (BTS) open label study[14] attempted to model real-life practice more closely by including a 6-month observation period before starting oral corticosteroid treatment. Patients in whom there was no evidence of spontaneous improvement after this time were started on treatment. These patients were then alternately allocated to one of two groups. One group were treated with steroids for at least 18 months (prednisolone 30 mg daily for 1 month, reducing by 5 mg every month to a maintenance dose of 10 mg daily) with the aim of achieving and maintaining maximal radiographic improvement; while in the second group treatment was limited to alleviating symptoms or managing deteriorating lung function. Patients were followed up for 5 years.

Patients in the first group showed greater improvements in symptoms, lung function and radiographic appearances than those in the second group. Average difference in vital capacity at the concluding review was 9% predicted. Of the 149 subjects recruited, 58 (39%) showed spontaneous radiographic resolution after six months and 33 (22%) needed steroids for symptoms. Most patients were white. Side-effects of treatment were frequent but mostly mild, leading to withdrawal in only two patients.

Symptom relapse on reducing or withdrawing steroids is well-recognised. A retrospective study[15] showed that relapse occurred more often in patients previously treated with steroids than in those who had experienced spontaneous resolution. The authors argued that steroid treatment itself could have contributed to disease prolongation. However most of the patients in this study were treated for extra-pulmonary disease, most were blacks and Afro-Caribbeans, and those experiencing spontaneous remission had milder disease initially. This question therefore needs addressing in a prospective study. Current UK guidelines on pulmonary sarcoidosis[16] conclude that we still do not know whether steroid treatment has a negative effect on longer-term prognosis.

A recent systematic review of steroid treatment in pulmonary sarcoidosis[17] included data from eight studies. Of 150 available studies, these were the only ones meeting the inclusion criteria and considered to contain valid data. Six studies examined oral steroids alone, one study used oral steroids then inhaled steroids, and one examined inhaled steroids alone. The authors concluded that oral corticosteroids improve CXR appearances after 6 to 24 months of treatment and result in small increases in vital capacity and diffusing capacity, although it is unclear whether these benefits persist after 2 years. These observations support the widespread view that steroids are not indicated in stage I disease unless lung function is declining. The authors commented that there are no data suggesting that steroid treatment influences long-term disease progression.

The starting dose of prednisolone in controlled studies has varied from 30 mg to 60 mg daily, usually tapering each month according to response, to an average of 10 mg daily maintained for 6 to 12 months before attempting slow withdrawal. Anecdotal observation suggests that in some patients, treatment is best continued for at least two years to prevent relapses. Alternate day dosing (with the dose kept equivalent to the average daily dose) has been suggested to limit side-effects[18] and shown in a controlled study to be as effective as daily treatment.[19] Such a regime is not always practical: diabetic patients may prefer daily dosing to maintain glucose control, and those who have difficulty remembering to take treatment may choose a once daily protocol.

## Treatment with inhaled corticosteroids

Selroos and colleagues first reported the value of inhaled budesonide in an open study of 20 patients with pulmonary

sarcoidosis.[20] Several later studies investigated the potential of inhaled steroids, either as first-line treatment or as maintenance after a response has been obtained with oral steroids. Only two studies, using budesonide, showed benefit.

A more recent study[21] compared outcomes after three months of prednisone followed by 15 months of inhaled budesonide with placebo. Corticosteroid therapy was of benefit, especially for those with parenchymal disease, and the benefit persisted for five years after stopping treatment.[22] In the systematic review already mentioned,[17] inhaled corticosteroid trials were small and the results inconclusive.

Taken together, current evidence thus suggests that inhaled steroids are less consistently effective than oral steroids in pulmonary sarcoidosis. This is unsurprising since they target the airways rather than the lung parenchyma, and it is generally agreed they should not be employed routinely.[23] They may have a role in maintenance treatment, or as steroid-sparing agents; they may also be of value in patients whose main symptom is cough and/or who have evidence of endobronchial involvement.

## Adverse effects of steroids

A number of recent studies indicate that adverse events such as weight gain, skin thinning, sleep disturbance, osteoporosis and neuropsychiatric disorders occur not infrequently in patients taking corticosteroids, even in low dose.[24] They appear to depend on dose and duration of treatment, and recent data reinforce previous observations suggesting that glucocorticosteroids significantly increase the risk of infection. Steroid-induced diabetes is also a significant risk.

There are no specific guidelines on monitoring for adverse effects in sarcoidosis. Although serious adverse effects may occur without warning, some are potentially preventable by using the lowest steroid dose possible, careful monitoring, and appropriate prophylaxis. National formularies contain general prescribing information, and various professional organizations and charities provide patient information.

Evidence-based guidelines for preventing and treating osteoporosis have been published in several countries, mainly but not exclusively in Europe and North America.[25] Most address post-menopausal osteoporosis; a few deal with corticosteroid-induced osteoporosis.[26–28] Adler and Hochberg have reviewed osteoporosis in men and sarcoidosis.[26]

The American College of Rheumatology (ACR) recommends several interventions for preventing bone loss and fractures in patients taking prednisolone at a dose of 5 mg daily or more for over 3 months.[27] Calcium and vitamin D supplementation (1500 mg/day and 800 IU/day respectively) is advised, as are bisphosphonates. Weekly preparations, such as alendronate 35 mg/week for prevention or 70 mg/week for treatment, or risedronate 35 mg/week for prevention or treatment, are preferred. These guidelines advise replacing gonadal steroids in men if deficient, and using calcitonin if bisphosphonates are contraindicated or not tolerated. They recommend annual follow-up and initiation of an exercise program where possible. They also advise 24-hour urinary calcium excretion estimation where the above measures are instituted because of the risk of hypercalcuria with glucocorticosteroids. If substantial hypercalcuria is present (defined as calcium excretion exceeding 400 mg/day), the authors advise a thiazide diuretic with salt restriction.

UK guidelines on the management of glucocorticoid-induced osteoporosis,[28] endorsed by a number of national specialist medical societies including the BTS, advise measurement of bone mineral density (BMD) to assess fracture risk in patients in whom there is a history of exposure to, or an intention to treat with, oral corticosteroids for three months or more. In those with a history of fracture, other secondary causes of osteoporosis should also be excluded. In those without a previous fracture and a T score above 0, reassurance and general measures are advised, and repeat BMD measurement is not indicated unless exceptionally high doses of glucocorticoids are required, as in for instance intravenous methyl prednisolone protocols.

If the T score is 0 to –1.5, general measures are advised and repeat bone density measurement in 1 to 3 years if steroids are continued. If the T score is –1.5 or lower, general measures and specific treatment are advised. General measures include reducing the steroid dose where possible and considering a steroid-sparing agent, nutritional advice with particular regard to calcium and vitamin D intake, regulating body weight, smoking cessation and avoiding alcohol excess, and assessing falls risk with further advice as appropriate. Specific treatments include alendronate, alfacalcidol, calcitonin, calctritiol, clodronate, cyclical etidronate, hormone replacement therapy, pamidronate and risedronate.

Adler and Hochberg address certain issues particularly relevant in sarcoidosis. Afro-Americans make up a large proportion of the sarcoidosis population and may be at reduced risk of glucocorticoid-induced osteoporosis.[26] However, since sarcoidosis can cause a vitamin D excess syndrome resulting from vitamin D activation in granulomas, hypercalcemia and hypercalcuria can occur and be made worse by supplementary calcium and vitamin D frequently recommended for other patients. These authors therefore advise measuring baseline serum and urine calcium and repeating measurements

4 to 8 weeks after starting calcium supplements, with subsequent monitoring. A study of BMD in women with sarcoidosis has shown that post-menopausal controls had higher BMD than untreated patients with sarcoidosis, suggesting that post-menopausal patients with sarcoidosis may be at increased risk of bone mineral loss.[29]

First reported in 2003, hundreds of cases of bisphosphonate-associated osteonecrosis of the mandible have now been described worldwide.[30] This complication can arise spontaneously or follow an invasive procedure such as dental extraction. Most cases have been associated with intravenous pamridonate and zoledronic acid, and length of treatment is a further risk factor, especially over 36 months. An initial dental examination with appropriate preventative dentistry should be considered before starting; while patients with concomitant risk factors should avoid invasive dental procedures while on treatment if possible.

A further consideration in sarcoidosis is that patients are relatively young, with females often of reproductive age. Since manufacturers advise against using bisphosphonates in pregnancy, physicians must either not prescribe these agents in females of child-bearing age or counsel them appropriately.

## Alternative immunosuppressive agents

A number of patients with severe or persistent sarcoidosis require treatment with alternative agents, usually in combination with corticosteroids but sometimes alone, either in those for whom corticosteroids are contra-indicated, or in those unable to tolerate the side-effects of steroids. The range of potential alternative immunosuppressive agents is wide and includes methotrexate, azathioprine, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, cyclosporin A, and chlorambucil, as well as agents which more specifically target TNFα, including pentoxifylline, thalidomide, infliximab and etanercept. Most of the published literature examining these agents consists of small case series with significant potential for bias, and many have primarily investigated the effects of these agents on extra-pulmonary, rather than pulmonary, disease. Only the most commonly used agents are reviewed here.

## Methotrexate

Methotrexate has been employed as a steroid-sparing agent for many years in the treatment of rheumatoid arthritis, and has recently emerged as one of the preferred second-line drugs for treating sarcoidosis. It is a folic acid analogue which inhibits dihydrofolate reductase and trans-methylation reactions. At low doses it has anti-inflammatory properties attributed largely to enhanced release of adenosine. Adenosine suppresses TNFα release from monocytes, macrophages and neutrophils, suppresses neutrophil reactive oxygen species release, and inhibits lymphocyte proliferation. A randomized controlled trial of methotrexate (10 mg once weekly) or placebo plus oral prednisolone in 24 patients, conducted over 1 year, showed that patients taking methotrexate required significantly less prednisolone in the second 6-month period.[31] However, the study was limited by a high drop-out rate, only 15 patients remaining in the study after 6 months, and methotrexate was no different to placebo on an intention-to-treat basis. Lung function, radiology and symptoms did not differ between the two groups.

Aside from teratogenicity, the major side-effects are hepatotoxicty and bone marrow suppression, and regular monitoring of liver function and full blood count is thus vital. There is uncertainty around the value of surveillance liver biopsy in patients exposed to methotrexate for prolonged periods. Many authors recommend co-treatment with folic acid to limit toxicity. A typical protocol is folic acid 5 to 10 mg once weekly, taken the day after methotrexate. Pregnancy should be excluded in females before starting treatment, and male and female patients receiving methotrexate must employ effective contraception. UK authorities advise continued contraception for at least three months after stopping the drug in males and females. North American advice is that pregnancy should be avoided for at least 3 months after treatment in male patients, and for at least one ovulatory cycle in females. Patients who experience troublesome systemic upset after taking the drug may benefit from dividing the once weekly dose into two twice weekly doses.

## Azathioprine

Azathioprine is a purine analogue which has been shown in case series to improve chest x-ray appearances and breathlessness.[32] Its exact mechanism of action is unclear, but it is converted to mercaptopurine, which affects RNA and DNA synthesis. Cellular immunity is suppressed to a greater degree than humoral immunity. There are no randomized controlled trials of azathioprine in sarcoidosis. A retrospective review suggested benefit in only 2 out of 10 patients,[33] while an open study analyzing 11 patients with chronic sarcoidosis treated with both azathioprine and prednisolone did suggest benefit.[34] All patients had significant symptomatic relief and showed improved radiographic and physiological parameters, without experiencing serious side-effects, despite reducing

their prednisolone dose to 0.1 mg/kg/day within two to three months of starting the study. Cytokine release in bronchoalveolar lavage was reduced. The authors commented that a larger study was required to answer definitively whether azathioprine might be an effective steroid-sparing agent in sarcoidosis; a decade later such a study remains to be conducted.

Regular blood counts to check for myelosuppression, and liver function monitoring, are essential in patients taking azathioprine. Azathioprine is metabolized by the enzyme thiopurine methyltransferase (TPMT), and the risk of myelosuppression is increased in the minority of the population who are homozygous for low TPMT activity. Consequently many authors advise testing for TPMT levels before starting azathioprine, despite a paucity of evidence to support this practice.[35] Azathioprine should not generally be initiated during pregnancy as there have been reports of premature birth and low birthweight after exposure; spontaneous abortion has been reported after maternal or paternal exposure.

## Hydroxychloroquine

Hydroxychloroquine (like chloroquine) is an anti-malarial agent. Two randomized controlled trials have compared chloroquine and placebo in pulmonary sarcoidois.[36,37] In the earlier British study, 52 patients who had not received steroids but either had pulmonary infiltrates for 6 months and breathlessness, or progressive lung infiltrates for 6 months, or persistent infiltrates for 1 year, were randomized to receive chloroquine or placebo for 16 weeks. Chloroquine treatment conferred no benefit and greater side-effects. In the recent, Canadian, study, 23 patients received chloroquine 750 mg daily for 6 months, gradually tapering every two months to 250 mg daily. Eighteen patients were then randomized to a maintenance group or to an observation group. Patients randomized to the maintenance group had a slower decline in lung function and fewer relapses than those in the observation group. Side-effects were mainly limited to the high dose treatment phase. The authors conclude that chloroquine should be considered in chronic pulmonary sarcoidosis; in practice, hydroxychloroquine is preferred because it has lower ocular toxicity.

Hydroxychloroquine should be used with caution in liver or renal impairment, and regular blood count monitoring (to check for agranulocytosis and thrombocytopenia) and liver function is needed. The British Royal College of Ophthalmologists advises that patients should be asked about visual impairment before starting treatment, and that visual acuity should be measured and recorded. If eye disease is present, an ophthalmologist should be consulted before starting treatment. Patients should be asked about visual symptoms during treatment and visual acuity monitored annually. If treatment is required for over 5 years, individual arrangements should be made with the local ophthalmology service.

Hydroxychloroquine should be used in caution in glucose-6-phosphate (G6PD) deficiency as it may precipitate acute hemolytic anemia. As deficiency is highly prevalent in Africans, in whom persistent and severe sarcoidosis is more common, many physicians check G6PD levels before starting hydroxychloquine.

## Cyclosporin A

Cyclosporin A is a T cell suppressor which has been reported to improve neurosarcoidosis in two retrospective studies. However, a randomized controlled trial in 37 patients with pulmonary sarcoidosis treated over 18 months showed no benefit in terms of breathlessness or lung function, and side-effects were significantly greater in the treatment group.[38] Its use cannot therefore be recommended in pulmonary sarcoidosis.

## Cyclophosphamide

Cyclophosphamide is an alkylating agent which has been used with apparent benefit in cardiac and neurosarcoidosis, but there are no controlled studies in pulmonary disease. Routine use cannot therefore be recommended.

## Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an antiproliferative immunosuppressant like azathioprine, but is metabolized to mycophenolic acid, which has a more selective action than azathioprine. Several authors report employing MMF successfully as a steroid-sparing agent in extra-pulmonary sarcoidosis, but there are no controlled studies in pulmonary disease, and there are therefore currently insufficient data to recommend its use.

## TNFα inhibitors

Agents which more specifically target TNFα include thalidomide, pentoxifylline, infliximab and etanercept. Individual case reports and small series support the use of thalidomide in cutaneous sarcoidosis, but there are no studies in pulmonary disease. Teratogenic concerns strictly limit its drug in women of child-bearing age, and side-effects can be troublesome. Pentoxifylline in high doses has been shown to improve lung function in mild pulmonary sarcoidosis.[39]

The TNFα inhibitor infliximab was first reported to be useful in refractory cutaneous and pulmonary sarcoidosis

in 2001. Since then a series of case reports and small series have reported the effectiveness of infliximab for treating various manifestations, including skin, eye, brain, lung, sinus and muscle involvement. Two larger studies were reported in 2006. The first, by Doty and colleagues,[40] was a retrospective study of ten patients with sarcoidosis refractory to conventional agents. Six patients had lung involvement although the indication for using infliximab in these patients was extra-pulmonary disease. Nine patients reported symptomatic improvement with infliximab treatment, and all demonstrated objective evidence of improvement. In five of six patients taking concomitant corticosteroids the dose was reduced. The authors did not comment on lung function or radiology. They nevertheless concluded that infliximab appeared safe and effective in refractory sarcoidosis.

The second study, conducted by Baughman and colleagues,[41] was a phase II, multi-center, double-blind, placebo-controlled clinical trial in which patients were randomized in a 1:1:1 ratio to receive intravenous placebo, infliximab 3 mg/kg, or infliximab 5 mg/kg at weeks 0,2,6,12, 18 and 24. Patients were followed through to week 52. 138 patients were randomized; 44 completed the placebo arm, 46 completed the infliximab 3 mg/kg arm and 45 patients completed the infliximab 5 mg/kg arm. In all cases the indication for entering the study was refractory pulmonary disease. Patients in the infliximab groups combined had a mean increase in forced vital capacity (FVC) of 2.5% predicted at week 24. Post-hoc exploratory analyses suggested that patients with more severe disease (longer disease duration, lower FVC or more symptoms) seemed to benefit the most.

Although these benefits appear modest, they would be significant in patients with life-threatening fibrotic disease who would potentially also be candidates for transplantation. Even stability in such patients represents a significant treatment response, and improvement would be exceptional.

Etanercept has not been found to be as effective in sarcoidosis, possibly because infliximab achieves greater tissue penetration and cell mediated lysis of TNF-secreting cells. Infliximab may therefore be considered in life-threatening pulmonary sarcoidosis when all other options have been exhausted. It is expensive, and patients need careful assessment beforehand for evidence of tuberculosis.

## Adverse effects of immunosuppression

Opportunistic infections are a potential consequence of immunosuppression. Prophylaxis against pneumonia caused by *Pneumocystis jiroveci* should be given to all patients with a history of the infection, and should be considered for severely immunocompromised patients. North American guidelines for preventing opportunistic infection in HIV-infected individuals,[42] endorsed by the British Infection Society, provide the basis for current recommendations. Oral co-trimoxazole is the drug of choice for prophylaxis, either 960 mg daily or three times a week. The dose can be reduced to 480 mg daily to improve tolerance. In patients unable to tolerate co-trimoxazole, nebulized pentamidine is effective, as is oral dapsone; atovaquone has also been employed. Co-trimoxazole and dapsone can cause bone marrow suppression and skin rashes among other side-effects. Neither North American nor British sarcoidosis guidelines recommend pneumocystis prophylaxis routinely in otherwise immuno-competent patients.

## Lung transplantation

A small number of patients with severe and progressive pulmonary sarcoidosis, despite exhaustive medical therapy, may be candidates for transplantation. Patients must be assessed for the potential presence of bronchiectasis, right ventricular impairment, infection, and mycetomas before proceeding.

Sarcoidosis patients represent around 3% of all transplant recipients in the USA.[43,44] In these series patients with sarcoidosis were no more likely to die than those undergoing transplantation for other reasons. African-Americans, however, were nearly 50% more likely to die. Possible reasons include reduced access to healthcare before and after surgery, increased graft loss due to immunological hyper-responsiveness, and greater major histocompatibility polymorphism. Similar findings are reported in the setting of renal and liver transplantation.[43]

Small series report 1-year survival figures of 62% to 72% and 4- to 5-year survival of 46% to 56%.[45,46] In 2008, the International Society for Heart and Lung Transplantation reported on survival for 506 sarcoidosis patients transplanted between January 1990 and June 2006.[44] Five-year survival was 51% and 10-year survival 31%. For comparison, 5- and 10-year survival in recipients with cystic fibrosis was 56% and 39%, and 45% and 21% respectively in recipients with idiopathic pulmonary fibrosis. Sarcoidosis is the most common disease to recur in transplanted lung, with reported recurrence rates of 35% to 62.5%,[45,47] but appears to have a good prognosis, often being asymptomatic and self-limiting.

## Current guidelines on sarcoidosis

A decade ago the American Thoracic Society (ATS), European Respiratory Society (ERS) and the World Association of

Sarcoidosis and Other Granulomatous Disorders (WASOG) jointly published a statement on sarcoidosis.[1] There was agreement that steroids are effective short-term but it was also emphasized that it is not known whether they alter the natural history of the disease, or for how long treatment should continue. The authors concluded that patients with progressive symptomatic disease, or asymptomatic patients with infiltrates on CXR and progressively worsening lung function, should probably be treated.

The ATS/ERS/WASOG review suggests an initial dose of 20 to 40 mg/day for pulmonary sarcoidosis, or the equivalent taken alternate days, and further evaluation of response after 1 to 3 months. In steroid responders it advises gradual tapering of the dose to 5 to 10 mg/day (or an equivalent alternate day dose), and treating for at least 12 months. It suggests that inhaled steroids may be of value in airway disease. In patients who fail to respond to steroids after three months, it suggests considering other reasons for failure such as the presence of irreversible fibrosis, noncompliance, or inadequate dosage.

The 2008 British Thoracic Society (BTS) interstitial lung disease (ILD)[16] guidelines conclude that treatment is not indicated for asymptomatic stage I disease, nor in asymptomatic patients with stage II or III disease with mild lung function abnormalities and stable parameters. They recommend oral corticosteroids as first-line therapy in patients with disease progression (as indicated by radiology or lung function) or significant symptoms. The authors recommend an initial dose of 0.5 mg/kg/day for 4 weeks, subsequently reduced to a maintenance dose which controls symptoms and disease progression, for a period of 6 to 24 months. Inhaled steroids are not recommended as initial or maintenance treatment, but may be considered for symptom control in patients with troublesome cough. Table 2 summarizes the main points from the two guidelines.

Bisphosphonates are advised as appropriate to minimize steroid-induced osteoporosis. Alternative immunosuppressants are recommended when corticosteroids are not controlling the disease or when side effects are intolerable, with methotrexate the agent of choice. Since low carbon monoxide transfer factor (TLCO) measurements predict survival in interstitial lung disease, they are a useful guide to the timing of referral for lung transplantation. British guidelines recommend that patients with end-stage pulmonary disease and a TLCO of $<$39% predicted should be considered by the regional transplant center.

In summary, there is agreement that oral corticosteroids should be considered in patients with severe, persistent or progressively worsening respiratory symptoms, or declining lung function. Severe symptoms are those which interfere with essential aspects of the patient's daily life, such as work or caring for young children. Many physicians would monitor lung function (VC and TLCO) for 6 months before deciding that there is progressive deterioration. There are no absolute cut-offs to determine when treatment is necessary, but most clinicians would regard a fall in VC of 10% to 15% and/or TLCO of $>$20%, confirmed more than once, as significant. There is agreement that neither oral nor inhaled corticosteroids are indicated in asymptomatic patients in the absence of other organ involvement.

The initial dose of oral prednisolone recommended by the ATS/ERS/WASOG guidelines is 20 to 40 mg daily; BTS guidelines suggest a slightly higher dose of 0.5 mg/kg/day. ATS/ERS/WASOG guidelines recommend further evaluation after one to three months; BTS guidelines advise review after 4 weeks. There is agreement that, provided the patient responds, the dose should then be reduced gradually to a maintenance dose.

ATS/ERS/WASOG guidelines suggest 5 to 10 mg daily as maintenance (or an equivalent alternate day dose) while BTS guidelines suggest a maintenance dose which will control symptoms and disease progression. ATS/ERS/WASOG guidelines advise treating for at least 1 year.

**Table 2** Summary of current guidelines for treatment of sarcoidosis

| Guidelines | Indications for treatment | Initiation: daily oral prednisolone dose | Maintenance: daily oral prednisolone dose | Inhaled steroids |
|---|---|---|---|---|
| ATS/ERS/WASOG | Progressive symptomatic disease, or asymptomatic with infiltrates on CXR and worsening lung function | 20–40 mg for 1–3 months before weaning | 5–10 mg for at least 1 year | May be useful in airway disease |
| BTS | Disease progression as indicated by radiology or lung function, or significant symptoms | 0.5 mg/kg for 4 weeks before weaning | As required to control symptoms and disease progression for 6–24 months | Consider for symptom control (cough) |

**Abbreviations:** ATS, American Thoracic Society; ERS, European Respiratory Society; WASOG, World Association of Sarcoidosis and Other Granulomatous Disorders; CXR, chest radiograph.

ATS/ERS/WASOG guidelines suggest that inhaled steroids may be of value in airway disease. BTS recommendations do not advise inhaled steroids as initial or maintenance treatment, but suggest they may have a place in managing selected patients to control cough.

With regard to monitoring for adverse effects, potentially serious side-effects are well recognized and the principles used in other clinical settings generally apply. National evidence-based guidelines for the prevention of steroid-induced osteoporosis provide valuable advice. Physicians may however wish to avoid prescribing calcium and vitamin D supplements in patients with sarcoidosis unless they also monitor serum and urine calcium levels. The dose of calcium and vitamin D can then be tailored according to these parameters. With bisphosphonates, clinicians should be aware of the risk of osteonecrosis of the mandible and be ready to advise patients to have an initial dental examination and appropriate preventive dentistry. When treating females of child-bearing age, they should also be aware that these agents are not recommended in pregnancy.

Current British ILD guidelines recommend considering other immunosuppressive agents when corticosteroids are not controlling the disease, or when side-effects are unacceptable, with methotrexate the agent of choice. Lung transplantation should be considered in end-stage pulmonary sarcoidosis.

## Conclusions

Sarcoidosis is the commonest ILD and is often managed by respiratory specialists. Despite experience of over 50 years using oral corticosteroids, their long-term benefits remain unclear, as is the value of inhaled corticosteroids. General management strategies include clear patient information and smoking cessation advice. Pulmonary rehabilitation, oxygen supplementation and palliative care may be appropriate in patients with severe pulmonary fibrosis. International guidelines recommend oral steroids in those with severe or worsening symptoms and/or infiltrates on CXR. There is broad agreement on the initial dose, subsequent tapering and length of treatment. Monitoring for adverse effects requires particular attention to steroid-induced osteoporosis. National guidance is usually applicable but physicians should be aware of individual patients' circumstances and may wish to amend advice accordingly. Alternative immunosuppressant agents and lung transplantation remain options for patients with severe disease.

## Disclosure

The author declares no conflicts of interest.

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