New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches

Robert P Baughman, Jan C Grutters

About half of patients with sarcoidosis will need systemic therapy for their disease. Oral glucocorticoids are the standard first-line treatment for sarcoidosis. With time, patients might develop substantial morbidity from long-term use of high doses of these drugs. We propose a step-wise approach to the management of pulmonary disease in sarcoidosis and provide details about how and when to use alternatives to glucocorticoids. The antimetabolites, such as methotrexate, azathioprine, leflunomide, and mycophenolate, are often used as alternatives to steroids. For patients who cannot be treated with low-dose glucocorticoids and an antimetabolite, anti-tumour necrosis factor (TNF) monoclonal antibodies have been shown to control disease. Unfortunately, anti-TNF drugs are associated with substantial toxic effects and in some cases are ineffective. The next step in treatment includes new strategies such as rituximab. A new regimen combining four antibiotics (levofloxacin, ethambutol, azithromycin, and rifamycin) has shown some promise in preliminary studies; however, the mechanism of action is unknown. Non-inflammatory effects of sarcoidosis, such as pulmonary hypertension and bronchiectasis, might also contribute to an increase in pulmonary symptoms. In those cases, alternative treatment strategies have to be considered.

Introduction
Pulmonary disease is identified in more than 90% of North American or European patients with sarcoidosis. About half of these patients will need systemic therapy, although the proportion of patients needing treatment varies widely from 20% to 80%. In specialty sarcoidosis clinics, nearly half of patients still need systemic therapy 5 years after initial diagnosis; 9% of these patients had chronic disease that necessitated increased treatment during the previous year. The treatment approach to sarcoidosis tends to follow a step-wise approach. Initial assessment of a patient includes determination of whether the patient has sufficient symptoms to warrant therapy. At least half of patients will not need this initial therapy. Those patients who do not need systemic therapy in the first 6 months have only a 10% chance that they will need long-term systemic therapy during the course of their disease. The usual pulmonary symptoms that suggest a need for treatment are cough, dyspnoea, or chest pain. For non-pulmonary disease, the symptoms are hypercalcaemia, ocular, neurological, or cardiac disease in addition to organ-threatening disorders such as liver or renal failure due to sarcoidosis.

Once the decision has been made to start systemic treatment, oral glucocorticoids such as prednisone or prednisolone are usually given. This treatment approach is based on the results of clinical trials that found steroids to be better than placebo for the treatment of pulmonary disease. For pulmonary disease, the usual initial daily dose is 20–40 mg of prednisone or its equivalent. The dose is then reduced every 2–3 months on the basis of treatment response or presence of toxic effects. Once a dose of 10 mg or less is achieved, most clinicians will maintain this dose for 3–6 months before lowering the dose again. However, in these circumstances the treatment can be long-lasting and associated with substantial toxic effects.

Figure 1 shows a decision tree regarding therapy options for symptomatic sarcoidosis. After initiation of prednisone or prednisolone, the patient is assessed for response to the drug. If the patient improves without toxic effects, then the dose of glucocorticoids is reduced. If the patient has disease progression or toxic effects initially or as glucocorticoids are tapered, then an antimetabolite should be considered. The full benefit of the antimetabolite therapy might take up to 6 months to be achieved. If during this time the patient is stable, reassessment of response to the antimetabolite should be done after 6 months, then the glucocorticoid dose should be tapered to the lowest tolerable dose and the antimetabolite continued. However, if during these 6 months the patient develops organ-threatening disease, or develops disease progression or toxic effects after 6 months, the clinician should consider giving an anti-tumour necrosis factor (anti-TNF) monoclonal antibody such as infliximab. At

Key messages
- The treatment of sarcoidosis is usually a step-wise approach.
- Although glucocorticoids are the most widely used initial therapy for symptomatic pulmonary disease, steroid sparing drugs are useful in at least half of patients.
- Of the four antimetabolites that have been proved steroid sparing in chronic sarcoidosis, methotrexate is the most widely used on the basis of published clinical studies and toxic effects.
- The monoclonal anti-tumor necrosis factor antibody infliximab is effective in refractory sarcoidosis.
- New treatments for sarcoidosis such as multitargeted regimens and mesenchymal stem cells need to be studied.
Initial therapy is prednisone or prednisolone. The alternative to anti-tumour necrosis factor therapy includes CLEAR; rituximab; corticotropin; mesenchymal stem cells; and vasoactive peptides.

**Figure 1:** Decision tree for treatment of symptomatic sarcoidosis

![Decision tree for treatment of symptomatic sarcoidosis](image)

In this point, if no disease progression or toxic effects develop, then the clinician should try again to taper the glucocorticoid dose. For patients who do not respond to an anti-TNF antibody, then clinicians should consider some alternatives, such as those discussed later in this Review.

The focus of this Review is to examine emerging treatment strategies for sarcoidosis as alternatives to glucocorticoids. Alternatives to corticosteroids have been developed for patients who need long-term courses of treatment. Risk factors for chronic disease needing treatment for more than 2 years include older patients, African-American people, need for systemic therapy at time of diagnosis, impaired lung function or moderate-to-severe dyspnoea at time of diagnosis, and some extrapulmonary manifestations such as neurosarcoidosis, cardiac sarcoidosis, or lupus pernio.

**Antimetabolites**

Methotrexate and azathioprine are the most widely used antimetabolite drugs for treatment of sarcoidosis. Methotrexate was first reported as an alternative to steroid treatment for sarcoidosis more than 50 years ago. Initial treatment regimens were short because of concerns about toxic effects in the pulmonary and hepatic systems. Subsequently, it was noted that it took more than 6 months before an objective improvement was reported with methotrexate treatment in sarcoidosis. Baughman and colleagues reported that methotrexate was steroid sparing compared with placebo after the first 6 months of treatment for acute pulmonary sarcoidosis. In some cases, patients could have systemic glucocorticoids completely withdrawn during treatment with methotrexate. In one study, methotrexate was the most widely used second-line drug for pulmonary sarcoidosis. However, major concerns with this drug have been related to hepatotoxic effects and pulmonary disease, although hepatotoxic effects in sarcoidosis seem to be present less often than originally estimated. Regular tests for liver function seem to be an adequate way to monitor for these adverse effects. Pulmonary toxic effects of methotrexate are another potential concern, but the risk is low if the drug is withdrawn at the first sign of potential toxic effects. A meta-analysis examined the risk of lung disease associated with methotrexate treatment in rheumatoid arthritis and noted an increased risk for respiratory infections (relative risk [RR] 1·11) and pneumonitis (RR 7·81 compared with other treatments). In a study of patients with sarcoidosis and deep-seated fungal infections, only those receiving prednisone alone or with methotrexate developed fungal infections. However, the rate of these infections for patients given prednisone and methotrexate for the duration of the study (18 months) was only 1·9%. Guidelines for methotrexate use in sarcoidosis have been developed by the World Association of Sarcoidosis and Other Granulomatous Disorders, and the drug seems to be safe as long as the patient is appropriately monitored.

Azathioprine has also been reported as an effective sarcoidosis treatment, although usually only in small case series. Compared with methotrexate, azathioprine is associated with more adverse side-effects leading to termination of drug treatment. In a retrospective study comparing the outcome of treatment with either methotrexate or azathioprine for sarcoidosis, Vorselaars and colleagues found similar efficacy for both drugs. However, azathioprine was discontinued more frequently because of adverse side-effects. Infections leading to discontinuation of treatment were significantly more widespread in patients receiving azathioprine versus methotrexate. Monitoring for leucopenia is important for the management of patients receiving azathioprine.

Since thiopurine S-methyltransferase is crucial for metabolism of the drug, tests for polymorphisms of this enzyme before treatment is initiated might be useful if the patient population is at risk for thiopurine S-methyltransferase deficiency. Other complications of azathioprine include nausea, pancreatitis, and hepatotoxic effects. The effects of azathioprine on the
with renal dysfunction. Leflunomide was developed as a less toxic alternative to methotrexate for patients with rheumatoid arthritis. The drug has been reported as an effective treatment for pulmonary and extrapulmonary sarcoidosis.\textsuperscript{20,21} In one study,\textsuperscript{21} changes in lung function were significantly improved with the addition of leflunomide treatment to background therapy of glucocorticoids or methotrexate. The drug functions synergistically when used with methotrexate for rheumatoid arthritis and the combination of leflunomide and methotrexate has been successful in patients with sarcoidosis.\textsuperscript{20} Table 1 combines the response rates reported from two series of patients with chronic sarcoidosis given leflunomide alone or in combination with methotrexate.\textsuperscript{20,21} Leflunomide is associated with less nausea than methotrexate, although the incidence of leucopenia and hepatotoxic effects is similar to methotrexate.\textsuperscript{21} Leflunomide rarely causes peripheral neuropathy.\textsuperscript{19} Interstitial pneumonia has been reported with leflunomide, although the proportion of interstitial lung disease seems to be substantially less than that for methotrexate.\textsuperscript{21}

Mycophenolate mofetil has been reported as useful in the treatment of sarcoidosis, including pulmonary sarcoidosis,\textsuperscript{24,25} and is more effective than other antimetabolites for the treatment of patients with chronic ocular inflammation.\textsuperscript{30,31} Since methotrexate and leflunomide are excreted by the kidney, these drugs are contraindicated in patients with renal dysfunction. Some patients have responded to combined mycophenolate with infliximab for treatment of neurosarcoidosis.\textsuperscript{26} Whether other antimetabolites such as methotrexate are inferior to mycophenolate in this situation is unclear. Mycophenolate was developed as an alternative to azathioprine for immunosuppression after solid organ transplant. Both drugs have been used safely in patients with renal dysfunction.\textsuperscript{19} Mycophenolate seemed to have fewer toxic effects and was more effective than those caused by azathioprine in the transplant population. In a meta-analysis\textsuperscript{27} in patients with renal transplants comparing mycophenolate with azathioprine, leucopenia and nausea caused by mycophenolate were less frequent than azathioprine, but this drug was associated with increased risk for total infections, diarrhoea, abdominal pain, and vomiting.

Clinicians have four equally good options when choosing an alternative to antimetabolite therapies—methotrexate, azathioprine, leflunomide, and mycophenolate. Table 2 summarises the major and other substantial toxic effects of these four drugs. Unfortunately, antimetabolite comparisons of effectiveness are difficult. We are aware of only one study\textsuperscript{19} that systematically compared methotrexate with azathioprine as a first-line antimetabolite. One of the difficulties is that some studies report the response rate using defined criteria for each organ, such as a greater than 10% improvement in forced vital capacity (FVC) or greater than 50% reduction in the size of skin lesion.\textsuperscript{11,12} However, other studies\textsuperscript{28,29} have used a change in the rate of decline in pulmonary function before the start of therapy compared with change after new treatment. The response rate reported for each of these drugs seems similar. Therefore, the decision for which one to choose is based on potential toxic effects and clinician preference.

### Anti-TNF treatment

If prednisolone or antimetabolites, or both, do not work, targeted TNFα inhibition is a valuable next step in the treatment of severe sarcoidosis, especially in organ-threatening or life-threatening disease.\textsuperscript{28,29} Although the effect of anti-TNFα monoclonal antibodies in rheumatoid arthritis and Crohn’s disease has been well documented, scientific literature about these biological agents in sarcoidosis is scarce. Best results have been reported for infliximab and adalimumab. Other targeted TNFα inhibitors such as etanercept and golimumab have not shown positive outcomes in patients with sarcoidosis.\textsuperscript{28,29}

So far, two randomised controlled trials have investigated infliximab in sarcoidosis.\textsuperscript{22,23} The study by Baughman and colleagues\textsuperscript{22} in 148 patients with chronic.

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### Table 1: Response or toxic effects to leflunomide in patients with chronic sarcoidosis

<table>
<thead>
<tr>
<th>Leflunomide alone (n=32)</th>
<th>Leflunomide plus methotrexate (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response\textsuperscript{a}</td>
<td>12 (38%)</td>
</tr>
<tr>
<td>Partial response\textsuperscript{b}</td>
<td>14 (44%)</td>
</tr>
<tr>
<td>No response or toxic effects</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>

Data are n (%) and are from a combination of two case series of sarcoidosis patients;\textsuperscript{20,21} >90% improvement in target organ; >50% improvement in target organ. \textsuperscript{a},\textsuperscript{b}5–10% improvement in forced vital capacity for lung disease and greater than 50% reduction in lesion for a specific organ, for example a skin lesion or brain mass.

### Table 2: Antimetabolite therapy

<table>
<thead>
<tr>
<th>Antimetabolite</th>
<th>Level of evidence in sarcoidosis</th>
<th>Most common toxic effects</th>
<th>Rare but important toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Double-blind placebo-controlled trials, prospective case series, case reports</td>
<td>Nausea, mouth ulcers, leucopenia, hepatotoxicity, nausea, infections</td>
<td>Pneumonitis, teratogenic</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Prospective case series, case reports</td>
<td>Leucopenia, nausea, infections</td>
<td>Severe leucopenia, hepatotoxic effects, pancreatitis, skin cancer</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Double-blind placebo-controlled trials, prospective case series, case reports</td>
<td>Leucopenia, hepatotoxic effects, infections, alopecia</td>
<td>Pneumonitis, teratogenic, peripheral neuropathy, hypertension</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Case series</td>
<td>Nausea, diarrhoea, infections</td>
<td>Skin cancer</td>
</tr>
</tbody>
</table>
pulmonary sarcoidosis showed a significant improvement of 2·5% in forced FVC after six infusions of infliximab over 24 weeks.38 Whether this improvement was clinically relevant has been a subject of debate.39 A trial by Rossman and colleagues40 did not show a significant improvement in lung function, but only involved 19 patients. The results of an open-label trial in Netherlands showed the largest improvement in FVC in combination with significant improvement in quality-of-life measures after 26 weeks of infliximab in patients with sarcoidosis.35

In the study by Vorselaars and colleagues,35 56 patients with severe sarcoidosis were included who were not successfully treated with prednisolone or antimetabolite therapy, or both. All patients had evidence of persistent disease activity, measured by serum activity markers and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET uptake, which was part of routine investigations before initiation of anti-TNF therapy. After eight infusions of infliximab (5 mg/kg), mean improvement in FVC was 6·6% of predicted (p=0·0007).13 The maximum standardised uptake value on ¹⁸F-FDG-PET of the lung parenchyma at treatment initiation correlated strongly with lung function improvement after anti-TNFα therapy. Therefore, ¹⁸F-FDG-PET activity is predictive for treatment response in severe and refractory pulmonary sarcoidosis, and might have added value in the process of treatment choices for individual cases.14 Changes in ¹⁸F-FDG-PET might also be useful to monitor response to treatment (figure 2). Raised C-reactive protein at baseline and sarcoidosis might respond better to infliximab than other patients.36,37 Conversely, patients on 20 mg or more of prednisone, derived no further benefit with the addition of infliximab versus placebo treatment.38

The effectiveness of adalimumab in pulmonary sarcoidosis was shown in a small open-label study.39 Furthermore, several reports have noted the efficacy of this biological agent in non-pulmonary sarcoidosis, especially with uveitis and sarcoidosis-related skin disease.40,41 A paradoxical response, so-called sarcoid-like granulomatosis, might arise during treatment with adalimumab. This event has been noted with other anti-TNFα monoclonal antibodies and most widely with the receptor antagonist etanercept.42 Therefore, physicians prescribing these drugs should be well aware of the possibility of a paradoxical effect, and consider discontinuation in case of suspicion.

Other adverse effects of TNFα inhibitors should also be taken into account when treating with anti-TNFα monoclonals: infusion and anaphylactic reactions, risks of infection, reactivation of latent infections (eg, tuberculosis and fungal infections), autoimmune and neurological effects, and possible malignancy.28 Therefore, before treatment, patients should be screened for tuberculosis, aspergillosis, and viral infections, and regular clinical and laboratory checks for infection during treatment should be done. Further, a study43 has reported the development of paradoxical autoimmune disorders, which range from the formation of antinuclear antibodies to lupus-like syndrome, vasculitis, and new-onset psoriasis during treatment with anti-TNFα agents. Demyelinating disease, including multiple sclerosis, might also occur during the course of anti-TNFα treatment, although at very low incidence.44 Confusion, paraesthesias, ataxia, and new visual symptoms should alert physicians to this side-effect.

Anti-TNFα therapy with targeted monoclonal antibodies can also be complicated by immunogenicity—ie, the formation of antibodies against the biological agent. Hardly any data exist for the development of antibodies towards biologicals in sarcoidosis, but positive tests for anti-infliximab antibodies have been reported in nearly a third of cases.41 Serum antibodies against infliximab are associated with infusion and anaphylactic reactions and with reduced efficacy because of increased clearance or neutralisation of its activity.28 In other autoimmune diseases such as rheumatoid arthritis and Crohn’s disease, a low-dose of methotrexate or another immunosuppressant is preferably added to infliximab therapy to optimise response by suppression of immunogenicity. Some clinicians recommend use of low-dose methotrexate or similar antimetabolites in patients with sarcoidosis.28 Discontinuation and resumption of infliximab treatment is also thought to induce the formation of antibodies against this biological, which might possibly be preventable by long-term maintenance therapy.

Despite the absence of evidence, expert opinion and experienced-based recommendations for the use of targeted TNFα inhibitors in sarcoidosis support clinicians in the management of severe refractory sarcoidosis.29 Recommendations concern general aspects of TNFα

Figure 2: PET scan of a patient with sarcoidosis before and after 6 months of infliximab treatment
(A) Patient with sarcoidosis showing pulmonary, skin, and lymph-node involvement, arthritis of metacarpophalangeal joints, and osseous involvement of a phalanx, as indicated by increased ¹⁸F-fluorodeoxyglucose uptake (green arrows=skin and lymph nodes, red arrows=metacarpophalangeal joints of left hand). (B) The repeated PET scan after 6 months of infliximab therapy. No abnormal uptake can be seen in the skin, lymph nodes, lungs, joints, or skeleton.
Relapse was noted after discontinuation in 29 (62%) of the 47 patients; of these, 23 were retreated with infliximab. Median time to relapse was 11 months, and 25% relapsed within 4 months. Both the mediastinal maximum standardised uptake value of 6 or more on ¹⁸F-FDG-PET (hazard ratio [HR] 3.77, p<0.001) and serum soluble interleukin-2 receptor of 4000 pg/mL or more (HR 2·24, p=0.03) were significant predictors of relapse and suggest that attentive monitoring of patients meeting these criteria is advisable.

Future research on targeted TNFα inhibition is particularly focused on personalised medicine, optimisation of dosing by measurement of drug concentrations in the blood, and the appearance on the market of biosimilars, biological medical products that...
are a copy of the original product (eg, infliximab) but manufactured by different companies. With respect to personalised medicine, two developments have been made in sarcoidosis treatment. First, as already mentioned, is the use of $^{18}$F-FDG-PET in the identification of patients with severe refractory pulmonary sarcoidosis that might benefit most from anti-TNFα therapy or those who are more likely to relapse when the drug is withdrawn.21,22 Second is the potential role for pharmacogenetics to adapt treatment of TNF inhibitors to the patient’s needs. One study23 showed that TNFα Gly308Ala polymorphisms were predictive of response to infliximab therapy. Although noteworthy, this study needs to be confirmed by other groups.

Optimisation of the dose of TNFα inhibitors in the blood of patients with sarcoidosis might lead to better cost-effectiveness of these relatively expensive third-line drugs compared with current practice. The same advantage might also apply to biosimilars that are on the market, although copies of infliximab or adalimumab might function differently than the original branded version of the product because of differences in impurities or breakdown products, or both. Another example is the tests for HLA-DRB1*03 in the Swedish population who have Lofgren’s syndrome.44 Patients who were HLA-DRB1*03 positive rarely needed treatment after 6 months, whereas almost half of the HLA-DRB1*03-negative patients needed chronic treatment.45

Thalidomide, pentoxifylline, and apremilast are three immunomodulatory drugs with non-targeted TNFα inhibitory effects in sarcoidosis. Thalidomide reduces TNFα release from alveolar macrophages and therefore also reduces granuloma formation. This drug has mainly been used to treat sarcoidosis-related skin disease with complete or partial responses in most of the patients in open-label trials.47 However, a randomised, placebo-controlled trial did not show clinically significant improvement compared with placebo.48 In a small number of patients with chronic pulmonary sarcoidosis, varying results were reported,49 which makes recommendation of thalidomide as a third-line drug for pulmonary sarcoidosis difficult. Pentoxifylline and apremilast are phosphodiesterase type 4 inhibitors that have TNFα inhibitory activity. Pentoxifylline in particular has shown a steroid-sparing effect but patients have complained of severe gastrointestinal side-effects at doses of 1200–2000 mg per day.50 So far, apremilast was only efficacious in a case series of 15 patients with chronic cutaneous sarcoidosis.51

**Other drugs**

Concomitant levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR) has been reported as effective in treating cutaneous52 and pulmonary53 sarcoidosis. Figure 3 summarises the outcome of the 15 patients enrolled in an open-label trial of CLEAR for chronic pulmonary sarcoidosis.53 For patients who completed all 8 weeks of therapy, a significant improvement in FVC was reported; this result was associated with other measures of improvement, including improvements in 6 min walk distance, Borg dyspnoea index, and St George’s Respiratory Questionnaire score.54 However, nearly half of patients were unable to complete the entire 8 weeks of therapy. The most common reason for discontinuation of treatment was adverse events, including leucopenia, arthralgias, insomnia, and rash. In a single-blind, placebo-controlled study of CLEAR for cutaneous sarcoidosis,54 15 patients received CLEAR and 15 patients received placebo. After 8 weeks, a significant improvement was noted in skin lesions for patients who received CLEAR, whereas no change was seen for those who received placebo. For patients given the CLEAR regimen, four (27%) of 15 patients discontinued treatment because of adverse events. However, three (20%) of 15 patients given placebo also discontinued therapy because of adverse events.

The rationale for use of CLEAR was based on evidence that some cases of sarcoidosis might have been caused by an unidentified mycobacterium.55 However, these macrolides and fluoroquinolones have also been shown to have anti-inflammatory properties.56 8 weeks of treatment with the CLEAR regimen did lead to significant changes in gene expression of some inflammatory mediators.57 A study is in progress that is investigating the efficacy of CLEAR for the treatment of patients with chronic pulmonary sarcoidosis (NCT02024555). If treatment with CLEAR does prove efficacious, this study might also clarify the mechanism of action. Because of the highly toxic effects of various antibiotics, this regimen should still be regarded as a rescue regimen for use only when other treatments have not worked.

Rituximab has been reported as effective for treatment of sarcoidosis58,59 however, its mechanism of action is

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**Figure 3:** Clinical outcome of 15 patients with sarcoidosis in an open-label, prospective trial of concurrent levofloxacin, ethambutol, azithromycin, and rifampin.53

FVC=forced vital capacity.
unclear. The granulomas of sarcoidosis might be the result of an interaction between CD4 T cells and antigen-presenting cells, usually macrophages.1 Rituximab treatment in sarcoidosis led to a reduction in immunoglobulin and B-cell concentrations.5 Immunoglobulin deficiency can lead to a granulomatous disease. However, rituximab is also an effective treatment for this disorder.6 Rituximab treatment has been shown to normalise the function of T-regulatory (Treg) cells in several inflammatory disorders.7 Treg-cell function is abnormal in active sarcoidosis and normalises with resolution of disease, therefore the mechanism of action of rituximab might be due to the effect of the drug on Treg cells.8

Since the reg abnormalities were more striking in the local reaction, such as in the bronchoalveolar lavage cells,9 monitored changes in Treg-cell function with therapy would need serial BAL. Results from the study by Prasse and colleagues10 showed that vasoactive intestinal peptide treatment was associated with normalisation of Treg cells in the BAL fluid of patients with sarcoidosis. No difference was reported in FVC after 4 weeks of treatment with vasoactive intestinal peptide. However, the follow-up might have been inadequate to detect changes in physiological variables to accompany the immunological changes. A larger study with longer treatment duration than that of Prasse and colleagues’ study is needed to clarify the role of vasoactive intestinal peptide in treatment of sarcoidosis.

Another new treatment approach for sarcoidosis is to introduce mesenchymal-like cells because they can suppress T-cell function. Mesenchymal-like cells can be successfully used to treat Crohn’s disease.11 In a pilot study with placenta-derived mesenchymal-like cells,12 Baughman and colleagues treated four patients with refractory pulmonary sarcoidosis. Although no significant change in pulmonary function was noted, two patients had improvement in parenchymal infiltrates on their chest radiograph and a dose reduction in prednisone for a year after treatment. One patient had long-term remission of at least 2 years.13

All of these new treatment regimens have been reported in small series of patients. So far, these treatments seem restricted to those patients for whom conventional treatment has not been successful (figure 1). Additionally, these drugs have different toxic effects, so they might represent alternatives to anti-TNF treatments. Future studies should define the role of these regimens in chronic pulmonary and extrapulmonary disease.

**Non-inflammatory complications of pulmonary sarcoidosis**

Dyspnoea and cough are the most common symptoms of pulmonary sarcoidosis. Although granulomatous inflammation of sarcoidosis is often the cause of these symptoms, several other causes have been identified that might not be a direct result of parenchymal lung inflammation, including pulmonary hypertension, airway stenosis, bronchiectasis, mycetoma, congestive heart failure, fatigue, and myopathy. Recognition of these symptoms is important since they are unlikely to respond to anti-inflammatory therapy. Although prednisone might be useful to treat airway reactivity, the antimetabolites and biological drugs have not been shown to be effective in the treatment of most of these disorders.

Pulmonary hypertension is a common complication of advanced pulmonary sarcoidosis and its presence is associated with increased mortality.14 Even though some cases are due to left ventricular dysfunction, almost all cases are caused by precapillary pulmonary hypertension. Patients with precapillary pulmonary hypertension have increased mortality compared with those with left ventricular dysfunction.15

Several drugs are effective in the treatment of sarcoidosis-associated pulmonary hypertension.16 Most of the reports are retrospective case series, although some are prospective case series.17 The prospective case series of single agents showed an improvement in haemodynamics in some patients. However, these studies usually did not show an improvement in 6 min walk distance. Improved quality of life was reported by patients who have been treated for their sarcoidosis-associated pulmonary hypertension. Bosentan is the only drug that has been tested in a double-blind, placebo-controlled trial18 for this disease. A significant improvement in pulmonary artery pressure was reported for patients treated with bosentan but no improvement was seen in the placebo group. However, no significant difference in the 6 min walk distance was reported after 16 weeks of therapy with bosentan.19

A retrospective case series20 reported that, overall, treatment for sarcoidosis-associated pulmonary hypertension for more than a year could lead to improvement in some patients. The investigators concluded that most of the patients who had an improvement in 6 min walk distance had an FVC greater than 51% (the median of their study group).21 Since this type of hypertension occurs more frequently in patients with sarcoidosis and pulmonary fibrosis, the severity of the underlying fibrosis will also affect overall lung function. Patients with severe pulmonary fibrosis could die from their sarcoidosis whether or not they have sarcoidosis-associated pulmonary hypertension.

Sarcoidosis can also lead to large and small airway obstruction. Large airway stenosis is best identified by bronchoscopy, although CT scans and flow volume loops can also suggest presence of disease.22 Airway stenosis might respond to treatment with glucocorticoids if treatment is started within 6–12 months of onset of stenosis. Patients who have had stenosis for more than a year are unlikely to respond to anti-inflammatory therapy presumably because the lesions have become fibrotic; in that situation, airway dilation might be helpful.
Fibrotic sarcoidosis has been associated with increased mortality.1 Among the causes of death are infection and pulmonary hypertension. Patients with fibrotic sarcoidosis often have acute worsening events that respond to antibiotics and an increase in prednisone dose.2 Acute worsening events in sarcoidosis were more likely in patients with underlying bronchiectasis or those receiving more intense immunosuppression, such as with infliximab.3 These cases of acute worsening seemed to be self-limited and patients often returned to their baseline status after treatment. These events were distinctly different from the acute exacerbations noted in patients with idiopathic pulmonary fibrosis.4 The long-term outcome of patients with repeated acute worsening events is still unclear.

One outcome of pulmonary fibrosis is superinfection with Aspergillus.5 Aspergillomas can lead to death from massive haemoptysis. Traditionally, aspergillomas have been treated with amphotericin, either systemically or intracavitary. However, the introduction of itraconazole and voriconazole has changed the treatment of these formations. In patients with sarcoidosis and aspergillomas, a randomised trial reported that itraconazole treatment was associated with significant clinical (p<0.016) and radiological improvement (p<0.001) compared with the placebo group.6

Fatigue is a complaint of patients with sarcoidosis. This symptom can be caused by several factors, including pulmonary hypertension. Patients might have severe fatigue despite treatment with potent anti-inflammatory drugs such as prednisone and infliximab.7 The presence of fatigue might contribute to dyspnoea; neurostimulants have been reported as effective in treatment of sarcoidosis-associated fatigue. Lower and colleagues8,9 have studied two neurostimulants (methylphenidate and modafinil) in double-blind, placebo-controlled, crossover trials. Both drugs led to a 30% reduction in reported fatigue after 8 weeks of treatment, which was significantly better than in the placebo group.9 A small but significant improvement was reported in FVC after 8 weeks of treatment with d-methylphenidate but not with placebo.10 For patients with progressive disease despite treatment, lung transplantation is still an option. Although recurrence of granulomas can develop in the donor lung, organ failure due to recurrent sarcoidosis is rare. However, the survival rate after transplant for sarcoidosis is lower than most other disorders, such as emphysema and idiopathic pulmonary hypertension.11

Conclusion
The treatment of sarcoidosis has evolved over the past 10 years. New treatments are emerging as alternatives or replacements for glucocorticoids in patients with symptoms. PET scans have been useful in the assessment of responsiveness to anti-TNFα therapy. Future studies might identify other biomarkers to predict the need for initial or continued therapy. As more potent anti-inflammatory drugs have been used in sarcoidosis, subsets of patients who have pulmonary symptoms because of other causes are often identified and new treatments have been developed for these patients as well. Decisions with respect to the application of new treatment strategies in individual cases should therefore be preceded by thorough evaluation of the various causes of pulmonary symptoms, and also include an assessment of disease activity. Ideally, this work should be done in centres of expertise and in a multidisciplinary setting.

Contributors
Both authors contributed equally in the design and writing of this manuscript.

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