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EVIDENCE-BASED REVIEW

Treatments for pulmonary sarcoidosis ☆

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Received 2 April 2007; accepted 24 July 2007

KEYWORDS
Pulmonary sarcoidosis;
Corticosteroids;
Immunosuppressive and cytotoxic drugs;
Systematic review

Summary
Corticosteroids (oral or inhaled) are commonly used to treat pulmonary sarcoidosis; however, there is no consensus about when to start treatment, what dose of steroids to give and for how long. Immunosuppressive and cytotoxic agents (used in immunosuppressive doses) are used in addition to oral corticosteroids to treat multisystem and chronic sarcoidosis, or as steroid-sparing agents. We summarize the findings from two Cochrane systematic reviews that have examined the efficacy of corticosteroids and immunosuppressive and cytotoxic drugs in the treatment of pulmonary sarcoidosis. Studies of corticosteroids differed in outcome measures, dose of drug given and length of treatment. For many outcome measures, data could not be pooled for meta-analysis. Oral corticosteroids improved chest X-ray appearance over 3–24 months, with improvement in global score in one study. Little evidence was found of improvement in lung function or of any long-term disease-modifying effect. Follow-up data could not be analysed. Inhaled corticosteroids improved symptoms in one small study but not lung function or chest X-ray. Side-effects of steroids were not well reported. In the immunosuppressive and cytotoxics review, no data could be combined for meta-analysis. Data on lung function, chest X-ray and dyspnoea were largely inconclusive. Methotrexate had a steroid-sparing effect in one small study. Significant adverse events were associated with cyclosporine A, chloroquine and pentoxifylline. Evidence from randomized-controlled trials (RCTs) supporting the use of immunosuppressive and cytotoxic agents is limited.
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Contents

☆The following Cochrane reviews have been cited in this Evidence-Based Review. Paramothayan NS, et al. Corticosteroids for pulmonary sarcoidosis, Issue 2, 2005; Paramothayan NS, et al. Immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis. Issue 3, 2006.

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0954-6111/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.rmed.2007.08.010

Please cite this article as: Paramothayan S, Lasserson T. Treatments for pulmonary sarcoidosis. *Respir Med* (2007), doi:10.1016/j.rmed.2007.08.010

Introduction

Sarcoidosis is a common multisystem granulomatous disease that frequently involves the lungs and can result in pulmonary fibrosis. Certain populations have a higher incidence of the disease, and the course of the disease is more relentless, with higher mortality and morbidity.[1] The severity of lung involvement is assessed on the basis of symptoms (particularly dyspnoea and cough), changes on chest X-ray (staged from 1 to 4) and lung function. Patients may also complain of systemic symptoms such as lethargy and organ-specific symptoms.

Oral and inhaled corticosteroids are used widely to treat pulmonary sarcoidosis, but there is no consensus about when treatment should be started, what dose of steroids should be given and for how long. Corticosteroids are given to reduce symptoms and to minimize long-term effects of the disease. Immunosuppressive and cytotoxic drugs are also given to patients with multisystem sarcoidosis in order to minimize symptoms in chronic sarcoidosis and as steroid-sparing agents. Combinations of drugs are often given. All drugs, including oral corticosteroids, have significant side-effects, particularly when given over a long period of time, and careful monitoring of the patient is required.

Sarcoidosis runs an unpredictable course: spontaneous resolution can occur without treatment[2] and relapses can also occur. Studies in sarcoidosis should take this into account and also that steroid responsiveness may vary by baseline severity. Randomization, blinding and adequate allocation concealment are all important in trials in order to minimize bias, but may not be done well, or even reported in trials. Trials need to ensure that treatment and control groups share the same baseline characteristics and that there is a control arm. Many trials have failed to do this.

In this paper, we provide an overview of the evidence from randomized-controlled trials (RCTs) on the efficacy of corticosteroids (oral and inhaled) and immunosuppressive and cytotoxic drugs in the treatment of pulmonary sarcoidosis. This overview is based on separate reviews published in the Cochrane Library.[3,4]

Review methodology

Study inclusion criteria

Reviews included RCTs of adults with evidence of pulmonary sarcoidosis, judged where possible on histological evidence. Patients with other interstitial lung diseases were excluded. Trials looking primarily at non-pulmonary manifestations of sarcoidosis were not considered; patients with multisystem sarcoidosis and lung involvement were considered eligible.

Interventions

In the corticosteroid systematic review,[3] trials compared participants taking oral or inhaled corticosteroids with controls receiving placebo or no treatment (Table 1). In the immunosuppressives and cytotoxics review,[4] the treatment groups received chloroquine, methotrexate, cyclosporine A or pentoxifylline. The control groups received corticosteroids alone, placebo alone or placebo and corticosteroids (Table 2). No RCTs using azathioprine, hydroxychloroquine, chlorambucil, cyclophosphamide, tumour necrosis factor alpha (TNFα) or thalidomide were identified.

Outcome measures

Primary outcome measures were chest X-ray changes, lung function measurements (forced expiratory volume in 1 s

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Table 1 Details of included studies in the systematic review of corticosteroids in pulmonary sarcoidosis.[3]

Source (year)	Disease stage	Treatment arms			Sex	Age range (years)	Follow-up after treatment	Allocation concealment	Study quality (Jadad score)
		Active	Control	Treatment duration					
Alberts et al.[7]	1–3	Budesonide, 1.2 mg/day	Placebo	6 months	21 male 26 female	20–65	6 months	A	4
Baughman et al.[8]	1–4	Prednisone then fluticasone 880 mcg/day	Placebo	12 weeks	8 male 14 female	22–64	48 weeks	B	3
DuBois et al.[9]	2–3	Fluticasone, 2 mg/day (75% on oral steroids)	Placebo	6 months	17 male 26 female	18–65	None	B	3
Erkkila et al.[10]	1–2	Budesonide, 0.8 mg twice a day	Placebo	8–10 weeks	8 male 11 female	27–59	None	B	3
Israel et al.[11]	1–3	Prednisone, 15 mg/day	Placebo	3 months	23 male 60 female	21–40	1–11 years	B	3
James et al.[12]	Multisystem	Prednisolone, 20 mg/day	Placebo	6 months	42 male 33 female	0–60	None	A	4
Ludwig-Sengpiel et al.[13]	1–3	BDP, 800 mcg/day	Placebo	12 weeks	9 male 6 female	35 (mean)	None	B	5
McGrath et al.[14]	2–4	HFA-134a BDP, 1.6 mg/day	Placebo	6 months	11 male 20 female	18–65	3 months	B	3
Milman et al.[15]	1–3	Budesonide, 1.2/2 mg/day eight patients on oral steroids	Placebo	12 months	17 male 5 female	21–65	18 months	B	3
Pietinalho et al.[16]	1–2	Prednisolone, 10–20 mg for 3 months then budesonide, 1.6 mg for 15 months	Placebo	18 months	105 male 84 female	Not stated	18 months	B	3
Roth et al.[17]	1–3	40 mg prednisone then reduced by 5 mg/day	No treatment	12 months or 6 months (two groups)	87 male 85 female	20–69	3–14 years	B	1
Selroos and Sellergren[18]	2	Methylprednisolone, 4–32 mg	No Treatment	7 months	19 male 18 female	Not stated	4 years	B	1
Zaki et al.[19]	1–3	Prednisone, 40 mg for 3 months, then 20 mg	Placebo	2 years	25% male 75% female	All	2–4 years	B	3

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Table 2 Details of included studies in the systematic review of immunosuppressive and cytotoxic therapy in pulmonary sarcoidosis.[4]

Source (year)	Disease stage	Treatment arms		Treatment duration	Sex	Age range (years)	Follow-up after treatment	Allocation concealment	Study quality (Jadad score)
		Active	Control						
BTA[22]	2–4	Chloroquine 600 mg/day (8 weeks), 400 mg/day (8 weeks)	Placebo	4 months	21 female 31 male $n = 52$	All ages	8 months	A	4
Wyser et al.[24]	1–4	Cyclosporine A (7 mg/kg/day)+ declining doses of prednisone	Prednisone	6 months	24 female 13 male $n = 37$	Mean Age 37	18 months	B	2
Baltzan et al.[20]	2,3	Chloroquine (250 mg/day)	Placebo	6 months	10 female 8 male $n = 18$	29–67	19.7 months (6–48)	B	3
Baughman et al.[21]	1–3	Methotrexate (10 mg/day)+ prednisone (40 mg/day)	Placebo+ prednisone (40 mg/day)	12 months	10 female 14 male $n = 24$	26–52	None	B	5
Manganiello et al.[23]	Not reported	Pentoxifylline (unspecified dose)+corticosteroids	Placebo+corticosteroids	24 weeks	Not reported $n = 27$	18–70	Not reported	B	2

[FEV_1], forced vital capacity [FVC], inspiratory vital capacity [IVC], diffusing capacity of carbon monoxide [D_LCO] and diffusing capacity of carbon monoxide corrected for lung volume [D_LCO/VA]) and steroid usage. Secondary outcomes were symptoms, adverse events and mortality. Outcome measures varied from trial to trial.

Literature search and identification of trials

Searches were carried out using MEDLINE, EMBASE, CINAHL and the Cochrane Controlled Trials Register of 218,352 RCTs up to May 2006 using pre-defined terms.

Methods of the review

Bibliographies of review articles and RCTs were searched for additional RCTs, and pharmaceutical companies and authors of RCTs were contacted for additional data and other published and unpublished studies. All studies, irrespective of language, were assessed by two reviewers to ensure they met the inclusion criteria. A third reviewer was to intervene if disagreement occurred, but none occurred. Each study was assessed, using pre-specified criteria, for the reliability of the diagnosis of sarcoidosis.

Statistical analyses

Where possible, trial data were combined with Review Manager version 4.2 (Revman, The Cochrane Collaboration, Oxford, England). Continuous data (data measured by scales such as symptom scores) were aggregated to generate weighted mean differences. Dichotomous data (end points that divide study participants into two groups such as 'improved' or 'not improved') were combined as a ratio of odds (OR). We measured statistical variation between the studies using the I^2-statistic,[5] which expresses in percentage terms the amount of variation between the trials over and above what would be expected by chance. Planned subgroup analyses included corticosteroid dose, disease stage and disease duration. Data from trials looking at different drugs were analysed separately.

Study quality

For each trial, the concealment of allocation and the overall methodological quality using the five-point Jadad score[6] (which evaluates the reporting quality of randomization, blinding and withdrawal) were assessed by two reviewers.

Description of studies

Corticosteroid review

In the corticosteroid review,[3] 150 citations were identified, with 13 RCTs of variable quality included. Authors were contacted for verification of methodological quality, randomization procedure and information on outcome data. Three responded with additional information. All included studies were randomized; methods of randomization were reported in three studies.[7,11,18] Eleven studies were double-blind but two[17,18] had a 'no treatment' control arm and one[17] recruited participants on an open-ended basis over 10 years. A total of 1066 participants were recruited; median sample size was 45 (range: 15–280). All participants were adults with pulmonary sarcoidosis; most were white males. Diagnosis of sarcoidosis was based on chest X-ray and

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histology in all studies but one.[18] Three studies[8–10] used participants with newly diagnosed sarcoidosis, and the others included disease of longer duration. Chest X-ray staging at baseline and primary end points varied between studies. All studies reported data on lung function; all except one[8] reported data on chest X-ray.

Three studies compared oral corticosteroids with placebo,[11,12,19] two studies compared oral corticosteroids with a control group on no treatment,[17,18] six studies compared inhaled corticosteroids with placebo,[7,9,10,13–15] and one study compared inhaled corticosteroids with placebo as oral corticosteroid sparing agent.[8] In two studies on inhaled corticosteroids,[9,15] some participants had received prior treatment with oral corticosteroids. One study[16] compared inhaled corticosteroid with placebo after oral corticosteroid versus placebo: participants randomized to oral corticosteroids received inhaled corticosteroids, and those randomized to oral placebo received inhaled placebo. Data could only be pooled for the first treatment period (oral corticosteroid vs. placebo) (Table 1).

Immunosuppressives and cytotoxics review

In the immunosuppressives and cytotoxics review,[4] 502 studies were identified by the search, but only five RCTs were identified, containing a total of 164 participants. Studies were small, with sample sizes ranging from 24[20,21] to 52.[22] Pulmonary sarcoidosis was diagnosed histologically in all studies except one.[22] Trials were randomized with a parallel group design. Four studies were double-blind[20–23] and one[24] an open label study.

Four different treatments were assessed in the five studies (Table 2). Two studies[20,22] had the control groups on placebo alone, two studies[21,23] had the control groups on placebo plus corticosteroids, and one study[24] had the control group on corticosteroids. Study duration varied from 16[22] to 24 weeks.[23] The average follow-up period was 19.7 months (6–48 months). In three studies,[21,23,24] participants were taking oral corticosteroids. The process by which corticosteroid dose was reduced was well reported in two studies,[21,24] but not in one study.[23] Two studies[20,22] assessed chloroquine treatment without concomitant corticosteroid therapy.

Outcomes

Chest X-ray findings and symptoms were reported in two studies[22,24] and lung function reported in all except one.[23] Two studies[21,23] reported the effect of treatment on concurrent corticosteroid use. All studies reported adverse events (Table 2).

Methodological quality of included studies

Corticosteroid review. See Table 1 for Jadad scores and Cochrane allocation concealment grades.[3] The differences in Jadad scores reflect differences in quality of reporting rather than in the methodological quality of the studies. Studies were of variable quality. Verification of randomization procedure was available for three studies.[11,13,18] In two studies,[17,18] the control group had no treatment; in the absence of adequate blinding, this may have distorted any treatment effect.

Immunosuppressives and cytotoxics review. See Table 2 for Jadad scores and Cochrane allocation concealment grades.[4] The overall quality of the studies was mixed. Details of intervention varied between studies; description of control arm was unclear in one study,[20] with no placebo arm in another study[24]; so blinding could not have fully occurred. Randomization procedures were not reported in any of the published papers but established following correspondence for one study.[21] Two studies were of high quality.[21,22] One study[22] obtained an allocation concealment grading of A, but the ages of participants at baseline differed significantly between the two groups: this was attributed to chance. One study[23] was an unpublished conference abstract of low quality with limited information. Withdrawals and drop-outs were well reported in all studies except one.[23] In one study,[21] the profile of each patient that withdrew from the trial was reported along with the reason for doing so.

Results

Corticosteroid review

Oral steroids versus placebo

On the basis of data from the three studies that could be combined,[12,16,19] a significant improvement in chest X-ray was found in the group treated with oral corticosteroids compared with the placebo group. The fixed-effects OR was 2.46 (95% confidence interval 1.59–3.79; $P<0.001$); the random effects OR was 2.68 (95% CI 1.25–5.76) (Figure 1). More patients in the control group had unchanged chest X-ray at the end of treatment compared with the group on oral corticosteroids. Patients in the control group had a significantly greater deterioration in chest X-ray compared with the group taking oral corticosteroids (OR 0.33; 95% CI 0.14–0.81). However, there was moderate-to-high inconsistency between the studies (I^2 60.9%). The duration of treatment varied between the studies (3–24 months), and may account for differences in response.

Two studies of low methodological quality[17,18] had control groups on no treatment, so results could not be combined with trials above. One small study[18] reported improvement in chest X-ray at 7 months in the corticosteroid group, but, by 24 and 48 months, this difference was no longer significant.

One study[11] recorded a global score of chest X-ray changes, lung function and symptoms (grouped together as a global outcome in an unspecified manner) in 83 patients, and showed an improvement with oral corticosteroids after 3 months compared with the control group. Sub-group analysis showed improvement in global score with Stage 2 and 3 disease but not Stage 1 disease. No significant difference was found between the treated and control groups in the number of patients whose global scores remained unchanged or deteriorated.

Results of lung function data from different studies[16,18,19] could not be combined. In one study of 159 patients treated with oral corticosteroids for 2 years, no significant differences were found in any measure of lung function (FEV_1, FVC and D_LCO as dichotomous data) between treated and placebo groups.[19] Subgroup analysis of the radiographic stages showed no differences. Two studies[16,18] measured

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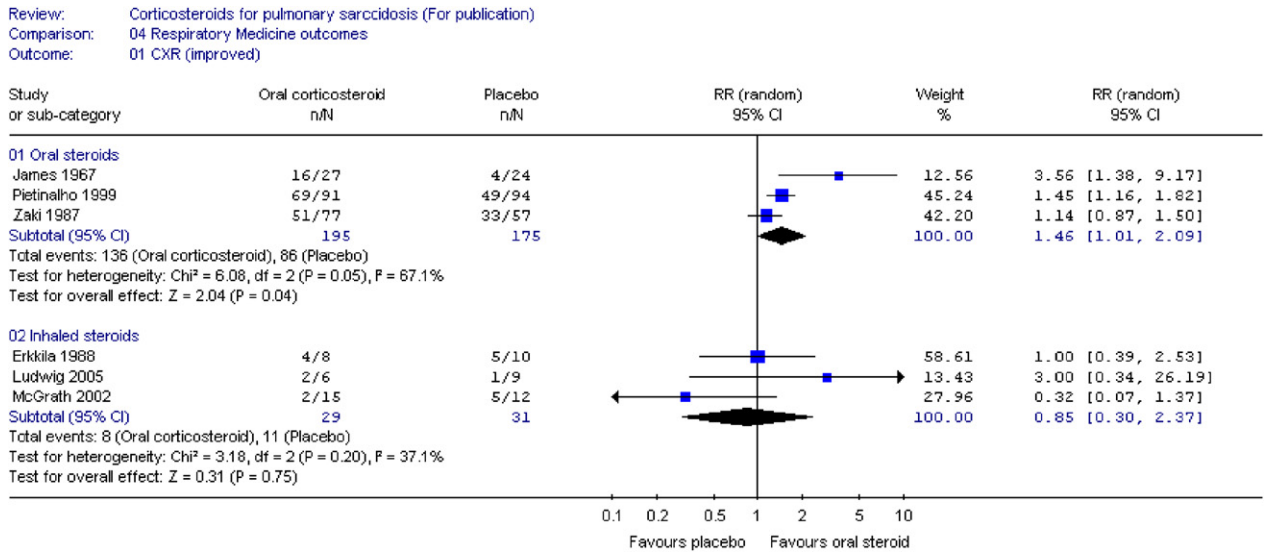

Figure 1

FVC and D_LCO as continuous data. In the small study of poor quality with no control arm,[18] there was an improvement in FVC and D_LCO with corticosteroids. Symptoms were not reported in any of these studies on oral corticosteroids versus placebo.

Inhaled steroids versus placebo

In four studies, patients had received no oral corticosteroids before receiving inhaled corticosteroids.[7,10,13,14] In three studies[9,15,16] a significant number of patients had received oral corticosteroids either as prior treatment or as part of the study protocol. Because data on chest X-ray and lung function were presented for all participants, regardless of whether participants had been treated with oral corticosteroids before study entry or not, the data from these studies could not be pooled.

No significant differences were found in chest X-ray between inhaled corticosteroids and placebo in three studies.[10,13,14] (Figure 1). Chest X-ray results from one study[7] could not be analysed. Inaccurate numbers were reported and no verification of data has been obtained.

Data on FEV_1 and D_LCO (% predicted) pooled from three small studies[10,13,14] and measurement of IVC (as % and litres) from two studies[7,13] showed no statistically significant differences between treated and control groups. One small study[10] measured D_LCO/VA (as dichotomous data) in 19 patients at the end of treatment with inhaled corticosteroids for 8–10 weeks and showed a significant improvement (+15%) in the treated group.

One study[7] found an improvement in the global clinical index (which included symptoms) in the treated group compared with placebo. Two studies[9,15] did not present data on symptoms separately for participants who had not received steroids before trial entry. No significant differences in symptoms were reported in any other study.

Inhaled steroids versus placebo as oral steroid-sparing agent

No data were presented on changes in chest X-ray.[8] No significant differences in FVC between treated and control groups were found. Median change in exercise capacity was reported but no details of the significance level were provided. No statistically significant differences were found between the fluticasone and placebo groups in any measure of symptom or in requirement for oral corticosteroids.

Several trials did not report adverse effects or corticosteroid-induced complications. It was not clear how prospective monitoring or patient self-report collected the data (Table 3).

Summary of results at follow-up

Treatment duration varied between studies, from 8 weeks[10] to 2 years.[19] Seven RCTs followed patients for 1–14 years from the end of the randomized-controlled period (Table 1). Data on chest X-ray changes, lung function, and symptoms were recorded but not reported in a systematic manner and could not be aggregated. No statistically significant difference in any outcome was shown in any study at the end of the follow-up period. Patients with improvement in chest X-ray, symptoms, global scores or lung function at the end of the treatment period did not maintain this improvement, relative to the control group, at follow-up. There was no standardized data collection after a period of corticosteroid withdrawal in any study.

Immunosuppressive and cytotoxics review

RCTs using methotrexate,[21] chloroquine,[20,22] cyclosporine A[24] and pentoxifylline[23] were identified. No data could be combined for meta-analysis (different drugs and end points). Data on lung function, chest X-ray scores and dyspnoea were largely inconclusive. Much of the data on medication usage and lung function were reported as

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Table 3 Details of patients randomized, excluded, withdrawn and lost to follow-up and reported adverse effects in the systematic review of corticosteroids in pulmonary sarcoidosis.[3]

Source (year)	Number of patients							
	Randomized	Completed	Excluded	Withdrawn	Lost to follow-up	Total withdrawn or lost to follow-up	Reasons	Adverse effects
Alberts et al.[7]	47	40	0	6	1	Budesonide group (4) Placebo group (3)	Five withdrew consent (two required oral prednisolone), one withdrew due to intercurrent disease	No budesonide related adverse events reported
Baughman et al.[8]	22	19	0	2	1	Placebo (2) Fluticasone (1)	Dropped out	No significant adverse events reported
DuBois et al.[9]	43	34	4	6	0	Fluticasone group (4) Placebo group (2)	Four excluded because of lack of diary card data; six withdrew due to serious adverse events; no explanation for discrepancy in numbers	Adverse events reported: fluticasone, 18/21 patients; placebo, 19/22 patients; chest infections, 'asthma', skin rash, hoarseness
Erkkila et al.[10]	19	18	0	1	0	Budesonide group (1)	Adverse events in treated group	Sensation of swelling of mouth
Israel et al.[11]	90	83	0	0	7	7	Not clear why seven patients did not complete treatment	None described
James et al.[12]	84	75	0	2	7	Prednisolone group (3) Oxyphenbutazone group (3) Placebo group (3)	One pregnant, one given steroids unintentionally, seven defaulted	Gross fluid retention, cushingoid changes
Ludwig-Sengpiel et al.[13]	15	15	0	0	0	0	NA	None described
McGrath et al.[14]	33	27	0	5	1	6	Two withdrew, one lost to follow-up, three required increase in oral therapy	Four developed oral candida, one hoarseness, one ecchymoses and purpura, one high-blood glucose levels, two reflux
Milman et al.[15]	21	17	0	4	0	Budesonide (3), Placebo (1)	Side-effects, found device cumbersome, pregnancy	Cough, sore throat, nausea
Pietinalho et al.[16]	189	154	0	35	0	Treatment group (16) Placebo group (19)	Seven withdrew consent, three due to adverse events, 16 due to treatment failure, five due to poor compliance, four due to other reasons	Adverse events: prednisolone followed by budesonide (2); placebo (1); decrease in serum cortisol below normal range; corticosteroid treated (11/92); placebo treated (1/97)
Roth et al.[17]	280	172	0	31	77	108	19 violated protocol; 12 had side-effects. Not explicit which groups these participants were allocated to	None described
Selroos and Sellergren[18]	37	32	2	5	0	All placebo group (5)	Two excluded due to non-compliance, five withdrew due to symptoms requiring prednisolone	Six developed moonface, seven weight increase, one hyperglycaemia, four hypokalaemia and one hypertension
Zaki et al.[19]	183	159	24	0	0	0	Lack of co-operation, relocation, concomitant clinical condition, or death	None described

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medians and ranges calculated with use of non-parametric statistical tests, indicative of uneven distribution. Two studies reported means and standard deviations on chest X-ray scores and lung function decline rates, respectively.[22,20] No data on mortality or quality of life were reported. Adverse events were reported in all studies. No sub-group analysis was possible.

Patients taking methotrexate[21] required significantly lower doses of corticosteroids than placebo after 12 months of treatment. Steroid usage was the primary end point, and data were presented as medians and ranges. There was no significant difference in steroid dose at 6 months between the groups. After 12 months, both groups required less prednisone but those on methotrexate required significantly less prednisone (median 8.3 mg/day [0.83–21.7]) than the control group (median 16 mg/day[11–22]): $P<0.001$. There was no difference between the groups in lung function (VC), symptoms (dyspnoea) or adverse events. No data on chest X-ray were reported.

Steroid usage and recurrence rate were lower in the pentoxifylline group[23] but with significant side-effects. This study was small, and randomization and blinding were not clear (Jadad score 2).

Treatment with cyclosporine A and prednisone was no better than prednisone alone in measurements of lung function. There was a statistically significant improvement in dyspnoea in both groups compared with baseline but no significant differences between the groups. No data on chest X-ray were reported. Significant adverse events were associated with cyclosporine A.[24]

Chloroquine reduced the decline rate in FEV_1 and D_LCO over 20 months in one study[20] but not in another.[22] In this study,[22] data on lung function were presented graphically with no distributional data, so could not be used. There were differences in lung function at baseline owing to differences in ages of participants in the groups. No differences were found between the treated and control groups in chest X-ray scores or dyspnoea at 12 months. Significant adverse events were observed with chloroquine.

Methodological limitations

Few trial data could be combined for meta-analysis: trials on the effects of corticosteroids used different outcome measures and presented lung function data in the form of dichotomous or continuous data. Much of the data were descriptive; for example, chest X-ray improved, unchanged or worsened. Oral and inhaled corticosteroid dose and type of inhaled corticosteroid varied between studies. Treatment duration varied from 8 weeks[10] to 2 years.[19] The only sub-group analysis possible was for radiological stage of disease. Follow-up data, up to a mean of 8 years after treatment, were available but unusable in the meta-analysis; follow-up studies were uncontrolled with no blinding, no common end point, collected data at random time points, and no information on patients lost to follow-up. Patients who had deteriorated after the treatment period were given oral corticosteroids and excluded from the study. This introduces a selection bias and a survivor effect, as those who were worst were excluded from the analysis.

A few small trials, of variable quality, using immunosuppressive and cytotoxic agents were found. Differences in treatment or outcome prevented combination of data. Efficacy was defined as regression of the disease (e.g. improvement in lung function), no deterioration in the disease or reduction in the maintenance dose of corticosteroids. No long-term follow-up data were available.

Discussion

Pulmonary sarcoidosis is characterized by an unpredictable course, with some patients showing spontaneous resolution, whereas others progress to lung fibrosis. Overall mortality from sarcoidosis is 1–5% usually from respiratory, cardiac or central nervous system disease. Lungs are affected in more than 90% of patients.[25] Because of the natural history of sarcoidosis, long-term outcome assessment is crucial in determining whether short-term treatment leads to long-term benefit.

Treatment of pulmonary sarcoidosis with oral corticosteroids for 6–24 months resulted in more patients with improved chest X-ray and fewer patients with deteriorating chest X-ray than the placebo group. The risk ratio for improvement in chest X-ray with oral corticosteroid was increased by 46% (95% CI: 1–109%), although the dose of oral corticosteroids varied between studies. Owing to the lack of controlled trials, there is no evidence that these improvements are maintained beyond 2 years or that corticosteroids have a disease-modifying effect. The improvement in chest X-ray is seen regardless of radiographic stage at baseline. A global score that aggregated chest X-ray, symptoms and lung function improved in the corticosteroid group; subgroup analysis showed improvement in Stage 2 and 3 disease but not Stage 1 disease. Pulmonary function data were not reported in a consistent manner across trials so it was not possible to pool the results. There was no convincing evidence of improvement in lung function. Data on other relevant outcomes, such as respiratory symptoms, exercise tolerance and adverse events were not reported.

Inhaled corticosteroids did not improve chest X-ray or lung function but improved global clinical index in one study.[7] As pulmonary sarcoidosis has an endobronchial component, inhaled corticosteroids may, in theory, improve symptoms such as cough. Most of the participants in the trials of inhaled corticosteroids had Stage 1 and 2 disease, so were perhaps less likely to show a significant improvement. There was no evidence that inhaled corticosteroids had an oral corticosteroid-sparing effect.

There is limited RCT evidence to support the use of immunosuppressive and cytotoxic drugs in pulmonary sarcoidosis. Most of the published data are anecdotal and any RCTs have been on small numbers of patients. Although used in immunosuppressive doses, these drugs have severe adverse effects and require close monitoring. One small study[21] found that methotrexate has a steroid-sparing effect after 12 months but with no improvement in lung function, chest X-ray or symptoms. One small study of poor quality found that pentoxifylline, a TNFα inhibitor, reduced steroid usage and recurrence but with severe side-effects.

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Practice points

- Patients with Stage 2 and 3 pulmonary sarcoidosis may benefit from oral corticosteroids for 6–24 months
- Oral corticosteroids are likely to improve chest X-ray and symptoms
- There is insufficient RCT evidence of any long-term benefits of oral corticosteroids; steroids should therefore be withdrawn after this period with careful monitoring
- There is insufficient RCT evidence that inhaled corticosteroids are effective in pulmonary sarcoidosis
- There is insufficient RCT evidence to recommend the use of any immunosuppressive or cytotoxic drug in pulmonary sarcoidosis

Research directions

- Trials using newer drugs with less severe side-effects (infliximab, thalidomide, mycophenolate mofetil, etanercept and leflunimide) need to be conducted
- In order to recruit sufficient numbers of patients this is likely to have to be a multi-centre trial
- Trial design must ensure that randomization, blinding and allocation concealment are rigorous and that the outcome measures include a well-validated symptom score, lung function and chest X-ray
- Long-term follow-up data, details of withdrawals, exclusions and adverse events must be reported
- Cochrane reviews are updated regularly. The next update will include all recent trials and incorporate those on infliximab

Acknowledgements

The authors thank Professor P.W. Jones, Professor E.H. Walters, Anna Bara, Jane Dennis, Steve Milan, Karen Blackhall, Liz Arnold, Bettina Reuben and Susan Hansen. Thanks also to Professor Selroos, Professor James, Dr. Baughman, Dr. Ludwig-Sengspiel and Dr. Pearson for additional data.

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Please cite this article as: Paramothayan S, Lasserson T. Treatments for pulmonary sarcoidosis. *Respir Med* (2007), doi:10.1016/j.rmed.2007.08.010