Corticosteroid Therapy in Pulmonary Sarcoidosis: A Systematic Review

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Sarcoidosis is a common multisystem granulomatous disorder. The lungs are frequently involved and pulmonary fibrosis may result. Black American and Afro-Caribbean populations have a higher incidence of the disease and may exhibit a more relentless course with higher morbidity and mortality. The severity of lung involvement is assessed on the basis of symptoms (particularly dyspnea and cough), changes on chest radiograph (which are staged from 1-4), and lung function. Spontaneous resolution can occur without treatment. Corticosteroids are given to reduce symptoms and speed resolution and in the hope of minimizing long-term effects (ie, modify progression of the disease). There is no consensus as to when corticosteroid therapy should be initiated, the dose, or treatment duration. Studies in sarcoidosis must take into account the spontaneous resolution that occurs frequently and the possibility that steroid responsiveness may vary by baseline severity. It is important to ensure that treatment and control groups share the same baseline characteristics and receive the same clinical management. This can be achieved only by randomization and blinding of the trialists to treatment allocation. Many studies have failed to

Context  Corticosteroids are used in pulmonary sarcoidosis to reduce symptoms and minimize long-term damage. Spontaneous recovery is a common feature. Both the decision to initiate therapy and the treatment response may be influenced by disease severity, so trials need to use a randomized controlled design.

Objective  To assess the effect of oral and inhaled corticosteroids on chest radiograph results, symptoms, pulmonary function, and long-term outcome in pulmonary sarcoidosis.

Data Sources  MEDLINE, EMBASE, CINAHL, and the Cochrane Controlled Trials Register were searched all years through December 2001. Bibliographies of review articles and retrieved articles were searched, and pharmaceutical companies and authors of identified trials were contacted for other studies. There was no language restriction.

Study Selection  Trials were randomized and included a control group. Participants were adults with histologic evidence of pulmonary sarcoidosis. Treatments included the use of oral and inhaled corticosteroids for at least 8 weeks. The search identified 150 studies; 9 met the inclusion criteria, but only 8 provided usable data.

Data Extraction  Two reviewers assessed trial quality using the Jadad score, which evaluates the quality of randomization, blinding, and reasons for withdrawal. Data were extracted and sent to primary authors for verification.

Data Synthesis  In patients with stage 2 and 3 disease, oral corticosteroids improved findings on the chest radiograph after 6 to 24 months (Peto odds ratio, 2.54; 95% confidence interval [CI], 1.69-3.81; P < .001). Forced vital capacity improved with oral corticosteroids (weighted mean difference [WMD], 4.2% predicted; 95% CI, 0.4% - 7.9% predicted) and diffusing capacity also improved (WMD, 5.7% predicted; 95% CI, 1.0% - 10.5% predicted). In 2 small studies of inhaled corticosteroids, there was no effect on chest radiograph and inconsistent effects on lung function in one and only a small improvement in symptoms in the other. There were no data following corticosteroid withdrawal to assess any disease-modifying effect.

Conclusions  Oral corticosteroids improved results on the chest radiograph following 6 to 24 months of treatment and produced a small improvement in vital capacity and diffusing capacity. Trials of inhaled corticosteroids were small and results too inconsistent to make firm conclusions concerning their efficacy. There are no data to suggest that corticosteroid therapy alters long-term disease progression.
could not be justified. This review aims to synthesize all available data obtained from randomized controlled trials (RCTs) to provide a least-biased estimate of the efficacy of corticosteroid therapy in pulmonary sarcoidosis.

**METHODS**

**Literature Search and Identification of Trials**

A search was performed using MEDLINE, EMBASE, CINAHL, and the Cochrane Controlled Trials Register of 218,352 RCTs through December 2001. The Medical Subject Heading, title, abstract, and key words were searched using the following terms: sarcoidosis and steroid or corticosteroid or prednisolone or prednisone or beclomethasone or budesonide or fluticasone. The RCTs were identified using the following terms: placebo or trial or random or double-blind or double blind or single-blind or single blind or controlled study or comparative study. The bibliographies of review articles and each RCT retrieved were searched for additional RCTs. Pharmaceutical companies were contacted for additional data and authors of identified RCTs were contacted for other published and unpublished studies. All trials were included, irrespective of language.

**Study Selection**

One reviewer assessed all retrieved abstracts, excluding those that were clearly not clinical trials using corticosteroids. We then assessed full-text articles for inclusion using the following criteria: (1) type of trial: RCTs or controlled clinical trials in which the noncorticosteroid interventions were standardized; (2) trial participants: adults with histologic evidence of pulmonary sarcoidosis (patients with other types of interstitial lung disease were excluded); (3) treatment: oral or inhaled corticosteroids given for a minimum of 8 weeks (the control group had to have received placebo or no treatment and interventions that used other drugs were not included); and (4) outcomes: at least 1 usable outcome of any kind.

Where there was doubt about the inclusion of a trial, a third reviewer was consulted. Two attempts were made to contact authors of included studies to verify data and check trial design. Where verification could not be obtained, the second reviewer extracted the data independently.

**Study Quality**

Two reviewers assessed allocation concealment for each trial. Overall methodologic quality was assessed using the 5-point Jadad score, which evaluates the quality of randomization, blinding, and reasons for withdrawal.

**Statistical Analyses**

Where possible, all trials were combined into meta-analyses using the Review Manager version 4.1 (Revman, The Cochrane Collaboration, Oxford, England). Continuous data were aggregated to calculate a weighted mean difference (WMD) using an inverse variance method. Dichotomous data were expressed as a Peto odds ratio (OR). Statistical significance for pooled data was accepted at P < .05. Random and fixed-effects models were both tested. Data from the fixed-effects models are presented, because there were no differences in the results between the 2 methods. Tests for heterogeneity in the size of response between studies were performed. We performed subgroup analysis if the tests for heterogeneity were significant at P < .10. Planned analyses included corticosteroid dose, disease stage, and disease duration.

**RESULTS**

**Description of Studies**

The search strategies identified 150 citations. Following review of their titles, key words, Medical Subject Headings, and abstracts, 50 full articles were retrieved. Several articles were excluded because they were not RCTs. For example, the study by Eule et al was a controlled study with a “no treatment” arm. It was neither randomized nor blinded, and there were no details of treatment withdrawal or dropout, so it was not possible to assess the potential for survivor effects. Nine RCTs met the inclusion criteria, but results from one could not be included because the results were presented in insufficient detail and no data were forthcoming from the author. Of the remaining 8 RCTs, 5 compared oral corticosteroids with a control group. Four compared inhaled corticosteroids with a control group. Two of these were performed in patients who received oral corticosteroids before inhaled therapy. The first phase of 1 of these studies is included among the 5 RCTs of oral corticosteroids. The patients in the remaining 2 studies of inhaled corticosteroids had not received prior treatment with oral corticosteroids. Full details of the included studies are contained in Table 1. Trials using oral corticosteroids date from the 1960s, but studies of inhaled corticosteroids in sarcoidosis have only been performed for little more than the last decade.

**Exclusions, Withdrawals, and Dropouts**

It was not possible to assess the size of the total pool of patients from which the participants were drawn for any of the included studies. Similarly, details of potential participants who either did not meet the entry criteria or were excluded from entry for other reasons were not available. There was inconsistent reporting of the numbers of patients who were excluded from analysis, withdrew from the study, or lost to follow-up (Table 2). Patients were withdrawn or excluded largely because of concomitant disease or deterioration requiring treatment with oral corticosteroids.

**Oral Corticosteroids**

Changes on the chest radiograph at the end of treatment were reported in 407 patients from 4 of the 5 trials that used oral corticosteroids alone. In these studies, the treatments and doses were as follows: methylprednisolone, 4 to 32 mg; prednisolone, 20 mg; prednisone, 20 to 40 mg; and prednisolone, 10 to 20 mg. The period of treatment ranged from 3 to 24 months. In
3 of the studies,9-11 patients in the control group were given a placebo, but in 1 trial8 the control group received no treatment. One of these studies included a heterogeneous group of patients with evidence of multisystem sarcoidosis, not just pulmonary disease.9 Combining all 4 studies, a \( \chi^2 \) test showed a significant difference in the response of the chest radiograph between corticosteroid-treated and control patients. When the chest radiograph responses were examined in detail, there was a significant improvement in chest radiograph findings at the end of the treatment period in the treated group compared with the control group (Peto OR, 2.54; 95% confidence interval [CI], 1.69-3.81; \( P < .001 \)) (Figure 1A). By contrast, more control group patients had an unchanged chest radiograph at the end of treatment compared with the treated group (Peto OR, 0.51; 95% CI, 0.33-0.77) (Figure 1B). Patients in the control group had a significantly greater deterioration in findings on their chest radiograph (Peto OR, 0.29; 95% CI, 0.14-0.61) (Figure 1C). There was no heterogeneity in the size of effect between trials in any of these comparisons (\( \chi^2 = 5.30 \) [\( P = .15 \)]) for radiograph improvement; \( \chi^2 = 3.78 \) [\( P = .29 \)] for radiograph unchanged; and \( \chi^2 = 1.83 \) [\( P = .61 \)] for radiograph deterioration). As such, the treatment effect appeared to be of similar size in all 4 studies.

A further study12 recorded chest radiograph changes, lung function, and symptoms in 83 patients. These clinical measures were grouped together as a global score, although the method by which they were combined was not explained in the study report and could not be obtained from the authors. After 3 months of treatment with prednisolone (15 mg/d), there was an improvement in the global score compared with the placebo group. Subgroup analysis showed an improvement in the global score in patients with radiographic stage 2 and 3 disease but not with stage 1 disease. There was no significant difference between the treated and control groups with regard to the number of patients whose global scores remained unchanged or had deteriorated.

Lung function data from the different trials could not be aggregated. One study measured forced expiratory volume in 1 second (FEV\(_1\)), forced vital capacity (FVC), and diffusing capacity of carbon monoxide (DLCO) in 159 patients after treatment with oral corticosteroids for 2 years.10 There was no significant difference between the treated and control groups in any of these measurements. Subgroup analysis of the different radiographic stages did not reveal differences between treated and control groups. Two other studies9,11 measured FVC and DLCO in 163 of 228 patients after treatment with oral corticosteroids for 3 to 7 months. There was a significant improvement in FVC (WMD, 4.2% of predicted; 95% CI, 0.4%-7.9% of predicted). The DLCO also improved (WMD, 5.7% of predicted; 95% CI, 1.0%-10.5% of predicted) (Figure 2).

### Table 1. Details of Included Studies

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Disease Stage</th>
<th>Treatment Arms</th>
<th>Treatment Duration</th>
<th>Sex</th>
<th>Age Range, y</th>
<th>Follow-up After Treatment</th>
<th>Blinding</th>
<th>Study Quality (Jadad Score)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberts et al,14 1995</td>
<td>1-3</td>
<td>Budesonide, 1.2 mg</td>
<td>Placebo</td>
<td>6 mo</td>
<td>21 M 26 F</td>
<td>20-65</td>
<td>6 mo</td>
<td>Adequate 3</td>
</tr>
<tr>
<td>DuBois et al,15 1999</td>
<td>2, 3</td>
<td>Mucinaceline, 2 mg</td>
<td>Placebo</td>
<td>6 mo</td>
<td>17 M 26 F</td>
<td>18-65</td>
<td>None</td>
<td>Adequate 4</td>
</tr>
<tr>
<td>Erkki et al,16 1988</td>
<td>1-2</td>
<td>Budesonide, 0.8 mg</td>
<td>Placebo</td>
<td>8-10 wk</td>
<td>8 M 11 F</td>
<td>27-59</td>
<td>None</td>
<td>Unclear 3</td>
</tr>
<tr>
<td>Israel et al,17 1973</td>
<td>1-3</td>
<td>Prednisone, 15 mg</td>
<td>Placebo</td>
<td>3 mo</td>
<td>23 M 60 F</td>
<td>21-40</td>
<td>5.3 y</td>
<td>Unclear 2</td>
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<tr>
<td>James et al,18 1967</td>
<td>Multisystem</td>
<td>Prednisolone, 20 mg</td>
<td>Placebo</td>
<td>6 mo</td>
<td>42 M 53 F</td>
<td>0-60</td>
<td>None</td>
<td>Adequate 4</td>
</tr>
<tr>
<td>Pietrasol et al,19 1999</td>
<td>1-3</td>
<td>Prednisolone, 10-20 mg for 3 mo followed by budesonide, 1.6 mg for 15 mo</td>
<td>Placebo</td>
<td>18 mo</td>
<td>105 M 84 F</td>
<td>Not stated</td>
<td>18 mo</td>
<td>Adequate 3</td>
</tr>
<tr>
<td>Selroos and Stellgren,20 1979</td>
<td>2</td>
<td>Methylprednisolone, 4-32 mg</td>
<td>No treatment</td>
<td>7 mo</td>
<td>19 M 18 F</td>
<td>Not stated</td>
<td>4 y</td>
<td>Inadequate 1</td>
</tr>
<tr>
<td>Zaki et al,21 1987</td>
<td>1-3</td>
<td>Prednisone, 20-40 mg</td>
<td>Placebo</td>
<td>2 y</td>
<td>25% M 75% F</td>
<td>Alt*</td>
<td>&gt;2 y</td>
<td>Unclear 2</td>
</tr>
</tbody>
</table>

*The Jadad scoring system ranges from 0 to 5.
†In the study, 33 patients were younger than 25 years, 72 patients were aged 25 to 34 years, 29 patients were aged 35 to 44 years, 23 patients were aged 45 years or older, and the age of 2 patients was unspecified.

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fluticasone propionate or placebo for 6 months. Three quarters (n=44) of these patients were receiving oral corticosteroids at the start of the study. There was no statistically significant difference between treated and control groups in any of the parameters measured: symptom scores, peak expiratory flow, FEV₁, FVC, DLCO, total lung capacity, and use of rescue bronchodilator medication. However, general health perception was improved. In another study, patients received either oral prednisolone or placebo for 3 months followed by inhaled budesonide or placebo-inhaled therapy. Oral corticosteroids followed by inhaled corticosteroids produced a significantly greater effect on the chest radiograph compared with placebo in patients with stage 2 disease but not with stage 1 disease. The authors concluded that, for stage 2 disease, sequential oral then inhaled therapy may provide an alternative to treatment with oral corticosteroids only.

Inhaled Corticosteroids—No Prior Oral Corticosteroids

There were 2 RCTs that assessed inhaled corticosteroids alone. None of the data were presented in a form that permitted meta-analysis. In 1 study, 47 patients, there was no improvement in inspiratory vital capacity, FEV₁, or DLCO after treatment with inhaled budesonide for 6 months. A combined score for self-reported symptoms (dyspnea, cough, malaise, and fatigue) improved by the end of treatment (P=.03). The second trial studied 19 patients treated with budesonide for 8 to 10 weeks. The number of patients whose chest radiograph results improved, remained unchanged, or deteriorated was the same in both groups. The DLCO, when reported as a continuous variable, did not improve. However, when corrected for lung volume

<table>
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<th>Table 2. Details of Patients Randomized, Excluded, Withdrawn, and Lost to Follow-up and Reported Adverse Effects</th>
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<td><strong>Source, y</strong></td>
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<td>Selroos and Sellergren, 1979</td>
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<td>Zaki et al, 1987</td>
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studied (DLCO/VA; diffusing capacity of carbon monoxide corrected for lung volume) and reported in terms of improved or not improved using a change of 15% increase as the criterion for improvement, there appeared to be a significant benefit in the treated group compared with the controls ($P = .04$). Of the budesonide-treated patients, 3 of 8 improved, compared with 0 of 10 in the placebo group, whereas 4 of 8 budesonide-treated patients remained unchanged as opposed to all patients in the placebo group.

**Subgroup and Quality-Based Sensitivity Analyses**

There were too few trials to permit analysis of the impact of trial quality on the calculated effect size or to permit any of our planned subgroup analyses.

**Uncontrolled Follow-up Data**

Patients in 5 RCTs were followed up for periods ranging from 6 months to more than 5 years from the end of the randomized controlled period of the studies. Four used oral corticosteroids$^{8,10-12}$ and 1 used inhaled corticosteroids.$^{14}$ Data on chest radiograph changes, lung function, and symptoms were recorded, but these were rarely reported in a systematic manner and none could be aggregated. None of these studies demonstrated a statistically significant difference between the treatment and control groups at the end of their respective follow-up periods. Patients who had shown an improvement in chest radiograph findings, symptoms, global scores, or lung function at the end of the treatment period did not appear to maintain this improvement, relative to the control group, at follow-up. There was no standardized data collection following a period of corticosteroid withdrawal in any study.

**Adverse Effects**

Several trials did not report adverse effects or corticosteroid-induced complications (Table 2). In these trials, it was not clear how prospective monitoring or patient self-report collected the data.

**COMMENT**

Treatment of pulmonary sarcoidosis with oral corticosteroids for a period of 6 to 24 months improved the chest radiograph findings, regardless of radiographic stage at baseline. Patients not
treated with corticosteroids were more likely to have deterioration in chest radiograph findings compared with those receiving prednisolone. In one study, a global score that aggregated chest radiograph results, symptoms, and lung function improved in the corticosteroid group. Subgroup analysis of that study showed an improvement in patients with 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. Within individual studies, there was usually no significant effect of oral corticosteroids, although 1 small study of low quality showed an improvement in DLCO and vital capacity in the treated group. In that study, subgroup analysis showed no difference in the effect of oral corticosteroids on DLCO between patients with different radiographic stages of the disease. Data on clinically important outcomes, such as respiratory symptoms and exercise tolerance, are not available.

Overall, results from these RCTs confirm the currently held view that patients with stage 1 disease (bilateral hilar lymphadenopathy alone) do not require treatment with oral corticosteroids, but those with interstitial lung disease (stages 2 and 3) may show radiologic improvement. There is little evidence for a beneficial effect on lung function. Sarcoidosis is commonly an endobronchial disease and can cause a troublesome cough, so inhaled therapy might be beneficial for this symptom. One study reported an improvement in global symptom score that included cough along with dyspnea, malaise, and fatigue, but this is the only RCT evidence for symptomatic benefit with this type of treatment. All clinical trials are potentially subject to biases that can influence the estimated treatment effect. Poor trial design, such as inadequate concealment of treatment allocation, may cause overestimation of the size of the apparent treatment effect. Scoring systems that attempt to categorize the level of randomization and blinding have been developed. The Jadad scoring system ranges from 0 to 5, based on randomization, blinding, withdrawals, and dropouts. Trials with a score of 2 or less have been reported to show consistently greater effects of treatment than those with a score 3 or more. Most trials (3/8) included herein had a score of 3 using this scale. In the context of trials of corticosteroid treatment for sarcoidosis, it is difficult to predict the effect of failure to blind the trialists and patients. In an unblinded study, physicians may have a low threshold for prescribing oral corticosteroids to patients in the placebo group, should they fail to improve spontaneously or appear to deteriorate. These patients would then be withdrawn from the study, causing the placebo group to be subject to survivor effects (ie, only those who did not deteriorate would remain in the study). This could minimize the difference between corticosteroid- and placebo-treated patients at the final assessment. Of the trials of oral corticosteroids that contributed to the meta-analysis, 2 (accounting for 60% of the patients) had evidence of adequate concealment. These 2 studies also showed the greatest proportion of corticosteroid-treated patients whose chest radiograph findings improved compared with placebo (Figure 1). There were too few trials to permit an adequate sensitivity analysis based on study quality, but we conclude that it was unlikely that our estimate of the efficacy of corticosteroids was inflated through lack of blinding to treatment allocation.

Recruitment bias will occur in all trials due to the operation of inclusion and exclusion criteria. Although trial reports may detail the criteria that were used, the value of this can be diminished by a failure to present details of all potentially eligible patients who were excluded because they did not meet the criteria or for other reasons. In the context of sarcoidosis studies, trialists may not have included patients in whom they thought that corticosteroids might be indicated at some stage, regardless of the entry criteria to the trial. Since none of the trials indicated the number of patients who were eligible for inclusion, it is not possible to determine whether there may have been selective enrollment of patients. In terms of radiographic disease stage at baseline, in the 4 oral corticosteroid studies that reported chest radiograph changes, 39% of patients had stage 1 disease, 49% had stage 2 disease, and 12% had stage 3 disease. This suggests that there was no major recruitment bias toward patients with less severe disease in these particular studies.

The biases that are usually of greatest concern are those that lead to overestimation of the treatment efficacy; however, it is not possible to predict the effect of selection bias in trials of sarcoidosis. For example, patients with few symptoms and/or mild radiographic disease (and thereby perceived by their physicians not to need corticosteroids) may have a greater likelihood of improving spontaneously. This may narrow the difference between the treat-
ment groups, especially if patients with more severe disease were less responsive to treatment due to more aggressive disease activity and more irreversible fibrosis. The survivor effect in placebo patients mentioned herein may also produce the same result.

Some recent large studies in sarcoidosis have been neither randomized nor blinded; for example, the British Thoracic Society multicenter sarcoidosis study. Patients were recruited to that study if, during a 6-month observation period, they had neither symptoms sufficient for their physician to commence prednisolone nor an improvement in the chest radiograph results. Of the 149 patients who entered the observation period, 33 were given oral corticosteroids for symptoms and 58 showed radiographic improvement. The remaining 58 patients were allocated alternately to either tapering-dose, long-term prednisolone (n=25), or selective, as-needed oral corticosteroids according to prespecified criteria (n=31). During the study, 20% of the selective patients had received prednisolone in a mean dose of 8.9 mg/d. This dose was almost identical to that in the long-term group. By the end of the 18-month treatment period, less than 20% of patients in either group were receiving oral corticosteroids. There were small differences in symptoms, chest radiographs, and lung spirometry that favored the long-term corticosteroid-treated group. This study was open to many different biases, but the size of the treatment effect was still small. Furthermore, the results were obtained in a highly selected group of patients, which limits the generalizability of its findings.

Some of these studies provided additional observations after the end of the randomized controlled period, but these data were subject to survivor effects, lack of adequate control, blinding, or standardization of measurement. Survivor effects may diminish the effect of treatment during follow-up; lack of blinding can lead to an overestimation of a treatment’s efficacy. Despite the potential for bias that may have favored corticosteroids, the follow-up studies showed no significant benefit of oral corticosteroids.

In conclusion, this systematic review of the RCT evidence for the effect of corticosteroids in sarcoidosis provides only limited guidance to physicians. Following oral corticosteroids, chest radiograph findings may improve in patients with more severe stage 2 and 3 disease, though it is not clear whether this is maintained beyond 2 years. There are no RCT data to test for a disease-modifying effect of corticosteroids. Such a trial would require a randomized treatment period, followed by withdrawal of therapy and detailed reassessment after an extended period, with the treatment allocation still concealed from patient and investigator. In view of the lack of evidence of sustained benefit and the known, but unquantified, adverse effects of oral corticosteroids in this population, corticosteroid therapy should be restricted to those patients in whom there is a clear clinical need. This can only be determined through careful clinical assessment with monitoring of chest radiographs and lung function. After a period of 6 months to 2 years, oral corticosteroids should be withdrawn under careful monitoring. The trials of inhaled corticosteroids were small and their results too inconsistent to make firm conclusions concerning the efficacy of this mode of corticosteroid delivery.

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Other Sources: Some analyses included herein are reported in a Cochrane Collaboration systematic review (Paramothayan NS, Jones PW. Corticosteroids in pulmonary sarcoidosis [Cochrane Review]. Cochrane Library. Oxford, England: Update Software; 2001:2). Cochrane Collaboration reviews are updated at regular intervals to take account of new RCTs.

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REFERENCES