Early Treatment of Stage II Sarcoidosis Improves 5-Year Pulmonary Function*

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Study objective: To evaluate the 5-year prognosis of patients with stage I and stage II newly detected (<3 months) pulmonary sarcoidosis treated immediately after diagnosis with prednisolone for 3 months followed by inhaled budesonide for 15 months. Thereafter, open follow-up without treatment.

Setting: Twenty pulmonary medicine departments in Finland.

Patients: One hundred eighty-nine adult patients, most of them with normal lung function, were randomized to treatment. One hundred forty-nine patients were followed up for 5 years: 79 patients with initial stage I disease and 70 patients with stage II disease.

Treatment: Oral prednisolone for 3 months followed by inhaled budesonide for 15 months (800 μg bid), or placebo tablets followed by placebo inhaler therapy. Thereafter, treatment only on an individual basis in the case of clinical deterioration.

Measurements: Yearly follow-up visits with chest radiographs, lung function tests (FEV₁, FVC), diffusion capacity of the lung for carbon monoxide (DLCO), serum angiotensin-converting enzyme (SACE), and serum and urinary calcium measurements.

Results: No initial differences were observed in chest radiographic findings between the active-treatment and placebo-treatment groups, either in patients with initial stage I or stage II(-III) disease. However, after the 5-year follow-up, 18 steroid-treated patients (26%) and 30 placebo-treated patients (38%) still had remaining chest radiographic changes. Placebo-treated patients more frequently required treatment with corticosteroids during the 5-year follow-up (p < 0.05). Steroid-treated patients with initial stage II(-III) disease improved more in FVC and DLCO (p < 0.05). No differences in reported adverse events or in SACE, serum calcium, or urinary calcium values were seen.

Conclusion: Immediate treatment of pulmonary stage II(-III) sarcoidosis—but not stage I disease—improved the 5-year prognosis with regard to lung function variables.

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Key words: angiotensin-converting enzyme; budesonide; chest radiograph; glucocorticosteroids; inhalation; lung function; prednisolone; prognosis; sarcoidosis

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; IL = interleukin; SACE = serum angiotensin-converting enzyme

Sarcoidosis is a systemic granulomatous disease usually affecting the respiratory tract. Treatment with glucocorticosteroids is recommended for patients with disturbing respiratory symptoms, clearly reduced lung function, and widespread radiographic infiltrates.¹ There is a general agreement that treatment improves symptoms as well as radiographic appearance and lung function test results, although the results of randomized, controlled trials are con-

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†A complete list of the members of the Finnish Sarcoidosis Study group is given in the Appendix.

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The differences in favor of active steroid treatment observed during therapy have in most studies not persisted during a follow-up. There is even an ongoing controversy whether, in fact, treatment with glucocorticosteroids may worsen the long-term prognosis.

One reason why clinical studies of corticosteroid-treated patients has been no different from untreated or placebo-treated patients could be that the included patients have had their disease for many years and irreversible changes unresponsive to treatment have already developed. That was the reason why we decided to study patients with newly detected pulmonary sarcoidosis, with the aim to investigate whether early treatment could influence the long-term prognosis. Our study therefore included well-defined patients with stage I or stage II pulmonary sarcoidosis with symptoms or signs of sarcoidosis for <3 months. However, symptoms were not a prerequisite, as symptom-free patients could be included. The study started with an 18-month treatment period consisting of prednisolone for 3 months (20 mg/d for 8 weeks, 15 mg/d for 2 weeks, and 10 mg/d for 2 weeks) followed by inhaled budesonide for 15 months (800 µg bid) delivered via Turbuhaler (Astra Zeneca Production; Södertälje, Sweden), or placebo tablets for 3 months followed by placebo inhaler therapy. The results of the treatment phase, previously reported, showed significant radiographic improvement for the first 6 months of treatment in stage I patients but not in stage II patients. In patients with initial stage I disease, no significant treatment differences were found for lung function test results or in tests for markers of disease activity. In stage II patients, diffusing capacity of the lung for carbon monoxide (DLCO) and serum angiotensin-converting enzyme (SACE) were significantly better at 18 months for the active-treatment group compared with the placebo-treatment group.

The reason why early treatment was considered ethical in all patients with newly detected pulmonary sarcoidosis even in the absence of symptoms or reduced lung function was the fact that the treatment administered was inhaled budesonide, which has a much improved safety profile compared with oral glucocorticosteroids. Inhaled budesonide provides sufficient tissue concentrations to produce an anti-inflammatory response as previously reported. The aim of this 5-year follow-up study was to investigate whether early treatment for 18 months had an influence on the long-term prognosis of patients with stage I and stage II pulmonary sarcoidosis irrespective of the initial lung function values of the patients.

Materials and Methods

Study Design

The 18-month treatment phase was a randomized, placebo-controlled, double-blind, parallel-group, multicenter study as previously described. The 5-year follow-up study was an open-label study extension.

Patients

The 18-month treatment phase included 189 randomized patients of both genders and ≥18 years old. They had newly detected (diagnosed within 3 months from the first symptoms or signs) radiographic stage I disease (bilateral hilar lymphadenopathy; n = 94) or stage II disease (parenchymal infiltrates with hilar lymphadenopathy; n = 84). Eleven patients were later reclassified as having had stage III disease (parenchymal infiltrates without hilar lymphadenopathy; n = 11) at the time of randomization. At baseline, normal lung function was seen in the majority of the patients. Only 23 patients had a FVC <50% of predicted and 12 patients had a DLCO <75% of predicted normal values. Ninety-two patients had been randomized to treatment with prednisolone followed by budesonide, and 97 patients were randomized to receive placebo. As previously reported, 154 patients completed the randomized, double-blind treatment phase and could be included in the follow-up study. The flowchart of patients with data from randomization to the end of the 5-year follow-up period is shown in Figure 1 separately for steroid-treated and placebo-treated stage I and stage II patients (the latter including the reclassified stage III patients).

Protocol

The investigational treatment was discontinued at 18 months. Thereafter, the patients visited the clinic once yearly (24 months, 36 months, 48 months, and 60 months after randomization) and underwent chest radiography, spirometry (FEV1, FVC), DLCO, and biochemical testing (SACE, serum and urinary calcium). The detailed methods for all investigational procedures have been previously described. The interpretation of all chest radiographs was performed at the end of the 5-year follow-up by one of the investigators (A.P.) without actual information about previous treatment codes.

In the case of deterioration or relapse, individually adjusted treatments could be started during the follow-up. The type and length of treatments were recorded. At the clinic visits, patients were asked questions about adverse events.

Ethical Requirements and Good Clinical Practice

Ethics committees at each study center approved the study, including the 5-year follow-up, before any study-related procedures were undertaken. Clinical research nurses of Meltola Hospital and one of the investigators (A.P.) monitored the follow-up study.

Data Management and Statistical Analysis

All data were entered at Meltola Hospital, the coordinating center, into a New Mathematical Statistics Package 5.0 database. The 5-year data were analyzed using New Mathematical Statistics Package 5.05 (Firma NMSP Statistik program; Lund, Sweden). The results were analyzed based on an all-patient-treated approach. A "last value extended" principle was used when data from the 24-month or later visits were available but not from the last visit.
For statistical comparisons, t tests and analysis of variance were used. Separate analyses were performed to investigate the influence of the initial stages (I or II) on the outcome. The radiographic stages were analyzed by a stratified Wilcoxon test with strata according to stage at visit 1 (randomization visit). The stage was also analyzed by two-way analysis of variance with treatment and center as well as their interactions as factors. In all presentations of statistical test results, a significant result refers to p values ≤ 5% (p < 0.05).

Results

Of the initial 189 randomized patients, 35 patients (16 steroid-treated and 19 placebo-treated) did not complete the 18-month treatment phase as previously reported. Of the 154 remaining patients, 149 patients participated in the follow-up part of the study. Five patients refused to take part in the follow-up. Figure 1 shows the initial randomization to treatment with corticosteroids or placebo, separately for patients with stage I and stage II(-III) pulmonary radiographic findings. The number of patients at the 5-year follow-up (n = 132) represents the total number of patients with complete data from randomization to the end of the follow-up period. However, all results are given for the 149 patients, including 70 corticosteroid-treated patients (31 women, 39 men) with a mean age of 39 years (range, 22 to 64 years) and 79 placebo-treated patients (38 women, 41 men) with a mean age of 41 years (range, 21 to 71 years). Randomization resulted in groups without statistically significant differences between them for age, gender, and initial chest radiographic stages.

Radiographic Findings

Table 1 shows the distribution of chest radiographic findings after the initial 18-month treatment phase and 5 years after randomization in 79 patients with initial stage I and 70 patients with initial stage II(-III) disease.

<table>
<thead>
<tr>
<th>Time/Stage</th>
<th>Initial Stage I Group</th>
<th>Initial Stage II(-III) Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corticosteroid Treatment</td>
<td>Placebo Treatment</td>
</tr>
<tr>
<td>18 mo</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Stage I</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Stage II</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Stage III</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>5 yr</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Stage I</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Stage II</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Stage III</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>
II(-III) disease. In stage I disease, 31 of 39 patients in the steroid-treated group and 27 of 40 patients in the placebo group showed normal chest radiographic findings. Parenchymal lesions developed in six patients in each group. No statistically significant difference was found between the groups.

The corresponding developments in the 70 patients with initial stage II disease are also shown in Table 1. The nine stage III patients—five patients in the active-treatment and four patients in the placebo group—have been included in this evaluation. Twenty-one of 31 steroid-treated patients and 22 of 39 placebo-treated patients had normal chest radiographic findings. Ten steroid-treated patients and 17 placebo-treated patients had abnormal chest radiographic findings after 5 years of follow-up. However, no statistically significant differences in the development of chest radiographic findings between the groups could be found.

**Lung Function Tests**

The baseline values used in the following comparisons are the values of those patients followed up for 5 years. The mean baseline values therefore differ slightly from the mean values given in the previous publication.5

For stage I disease patients, no statistically significant differences were seen for FVC or DLCO between steroid-treated and placebo-treated patients (Table 2). For patients with initial stage II(-III) disease, the treatment effects were different (Table 3). In the corticosteroid-treated group, a mean increase in FVC of 0.33 L was observed at 18 months and this level was almost maintained at 5 years. In the placebo group, no change in FVC was seen over time. At both time points (18 months, 5 years), the difference in change in FVC between corticosteroid-treated and placebo-treated patients was statistically significant (18 months, \( p = 0.018 \) and 5 years, \( p = 0.024 \), respectively). For DLCO, a mean increase was observed over time in the corticosteroid-treated group, whereas a mean decrease was seen in the placebo group. Also this difference in change over time was statistically significant (18 months, \( p = 0.034 \); 5 years, \( p = 0.028 \)).

In the subgroups of patients with impaired lung function at baseline, the differences in changes in FVC and DLCO between corticosteroid-treated and placebo-treated patients were greater than in the groups of patients with a normal lung function. The differences between these groups did not, however, reach statistically significant levels because of the low numbers in the groups of patients with impaired lung function.

On the whole, the mean increases in FVC and DLCO in the corticosteroid-treated group are modest. The mean results are, however, a consequence of the selection procedure, with most included patients having a completely normal lung function at randomization. For individual patients with an initially impaired lung function, the improvements in lung function tests are considered clinically important.

**Laboratory Test Values**

The mean SACE and serum calcium levels as well as urinary calcium values obtained at baseline, after 18 months of treatment, and after 5 years of follow-up are shown in Tables 2, 3 for initial stage I and stage II(-III) patients, respectively. No statistically significant differences were found between the groups.

**Discontinuations and Treatments Administered During the Follow-up**

After the 18-month treatment period, five patients never entered the follow-up phase. During the follow-up phase, corticosteroids had to be administered to 16 patients initially treated with placebo. In two patients initially treated with steroids, treatment had to be reinstituted because of a clinical relapse (Fig 2). The difference in frequencies between the groups in starting steroid treatment during the follow-up period was statistically significant (\( \chi^2 = 12.17; p < 0.001 \)).

The flow of patients during the entire 5-year study

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**Table 2—Lung Function and Laboratory Test Data in Patients With Initial Stage I Disease**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>18-mo Results</th>
<th>5-yr Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid Group</td>
<td>Placebo Group</td>
<td>Steroid Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, L</td>
<td>4.55 (1.18)</td>
<td>4.46 (1.07)</td>
<td>4.71 (1.12)</td>
</tr>
<tr>
<td>DLCO, mmol/L</td>
<td>9.48 (2.53)</td>
<td>9.34 (2.14)</td>
<td>9.86 (2.61)</td>
</tr>
<tr>
<td>min/H11005</td>
<td>S-Ca, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U-Ca, mmol/24 h</td>
<td>5.6 (3.1)</td>
<td>5.7 (2.6)</td>
<td>7.1 (2.8)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD). S-Ca = serum calcium; U-Ca = urinary calcium.*

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period is also illustrated in Figure 2. During the 18-month treatment phase, 19 patients discontinued the study as previously reported5 and 16 treatment failures were registered (6 in the active treatment group and 10 in the placebo group). During the subsequent follow-up period, 9 patients refused further follow-up visits and 18 patients required treatment with corticosteroids: 2 patients in the initial corticosteroid group because of relapses, and 16 patients initially treated with placebo. When the total number of treatment failures during the entire study is considered, the difference in outcome between the initial corticosteroid-treatment and placebo-treatment groups is also statistically significant ($\chi^2 = 10.49; \ p < 0.001$).

**Adverse Events**

No serious adverse events were reported during the follow-up, and there were no discontinuations of the follow-up because of adverse events.

**DISCUSSION**

Corticosteroids are considered to be beneficial in the treatment of pulmonary sarcoidosis, as their administration usually results in relief of respiratory symptoms and improvements in lung function and chest radiographic findings. Results of controlled clinical studies also show that both systemic9 and inhaled10,11 corticosteroid treatment influence cellular and biochemical findings, which appear to be important in the immunopathogenesis of the disease. However, reappearance of symptoms and radiographic infiltrates after discontinuation of treatment are frequent. As many as one third of treated patients have had recurrences within 2 years.12,13 It is also noteworthy that results of optimally designed dose-response studies are lacking, and little is known about the necessary duration of treatment.

Although initial improvements are seen, many controlled clinical studies have failed to demonstrate a persisting difference in lung function tests and radiographic appearance between corticosteroid-treated and untreated patients.14,15 The opinion has therefore often been expressed that corticosteroids do not alter the course of the disease and that treatment should be used only for relief of symptoms.2 However, the opposite opinion also exists: corticosteroids should be administered with the aim of preventing irreversible fibrosis to patients with pulmonary infiltrates and active disease regardless of the presence or absence of symptoms.16,17 Indeed, a number of clinical trials14,17–21 have clearly shown a beneficial effect of corticosteroid treatment compared with untreated or placebo-treated patients. The reason for the discrepancy in results between studies may be differences in patient populations, ethnic backgrounds, duration of disease with differences in the rates of spontaneous recoveries, and differences in study protocols, doses, and duration of treatment.

There are data to suggest that corticosteroids can impact on mechanisms important in the early stage of the pathogenic process. A number of genes, which play a role in the pathogenesis of sarcoidosis, can be modulated by corticosteroids. These genes are expressed soon after antigen triggering of CD4+ T cells and they include interleukin (IL)-2, interferon-γ, IL-1, and the IL-2 receptor, IL-2R.22 Other genes play important roles in the pathogenesis by influencing the expression of cell adhesion molecules (tumor necrosis factor-α) and leukocyte/monocyte proliferation and activation (granulocyte macrophage-colony stimulating factor, granulocyte-colony stimulating factor). They are also regulated by corticosteroids.22–25 It could be postulated that early intervention is of importance when treatment is administered in order to suppress an inflammatory and immunologically mediated processes. Therefore, the aim of this study was to include only patients with newly detected pulmonary sarcoidosis, ie, with symptoms or signs of

**Table 3—Lung Function and Laboratory Test Data in Patients With Initial Stage II (III) Disease; p Values Indicate Statistically Significant Differences in Changes Between the Groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline Steroid Group</th>
<th>Baseline Placebo Group</th>
<th>18-mo Results Steroid Group</th>
<th>18-mo Results Placebo Group</th>
<th>5-yr Results Steroid Group</th>
<th>5-yr Results Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>4.48 (0.88)</td>
<td>4.07 (1.03)</td>
<td>4.83 (0.98)</td>
<td>3.93 (1.03)</td>
<td>4.70 (0.98)</td>
<td>4.10 (0.97)</td>
</tr>
<tr>
<td>DLCO, mmol/min/kPa</td>
<td>9.17 (1.71)</td>
<td>8.65 (2.24)</td>
<td>10.05 (1.93)</td>
<td>8.50 (2.14)</td>
<td>9.73 (2.38)</td>
<td>8.45 (2.01)</td>
</tr>
<tr>
<td>SACE, U/mL</td>
<td>75 (50)</td>
<td>78 (80)</td>
<td>67 (38)</td>
<td>78 (63)</td>
<td>47 (34)</td>
<td>57 (39)</td>
</tr>
<tr>
<td>S-Ca, mmol/L</td>
<td>2.35 (0.08)</td>
<td>2.34 (0.12)</td>
<td>2.33 (0.11)</td>
<td>2.34 (0.10)</td>
<td>2.33 (0.12)</td>
<td>2.33 (0.12)</td>
</tr>
<tr>
<td>U-Ca, mmol/24 h</td>
<td>5.1 (2.7)</td>
<td>4.8 (2.7)</td>
<td>5.0 (2.8)</td>
<td>6.0 (3.4)</td>
<td>5.6 (2.3)</td>
<td>6.7 (2.9)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD). See Table 2 for expansion of abbreviations.*
the disease for < 3 months. Patients fulfilling this criterion and with radiographic stage I and stage II lesions were included irrespective of lung function status and presence or absence of symptoms. The results of the 18-month treatment period showed no differences in stage I patients in radiographic development, lung function test results, or levels of biochemical serum markers. The frequency of spontaneous improvements in the placebo group was also higher than estimated in the power calculation of the study. However, in patients with initial stage II disease (11 patients were later reclassified as corresponding to stage III), a significant effect was seen in DLCO values and SACE activities.

This 5-year follow-up part of the study demonstrated in patients with initial stage I disease no significant differences between treated and untreated groups in any of the outcome variables. The vast majority of the patients had normal chest radiographic findings and normal lung function. This result confirms previous observations that stage I patients should be followed up without treatment until spontaneous recoveries can be documented. In patients with initial stage II disease, the result was

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**Figure 2.** Flowchart for corticosteroid-treated and placebo-treated patients from randomization to the end of follow-up, showing the number of patients completing the study according to the protocol, as well as discontinuations and treatment failures.
different. Although no significant differences in chest radiographic developments could be detected, the differences in lung function tests were statistically significant. These differences also appear to be clinically relevant, indicating the value of early intervention with corticosteroids. There was no difference in the numbers of patients discontinuing the study during the initial treatment phase in the steroid-treated and the placebo-treated groups, respectively. During the follow-up phase, significantly more patients in the placebo group had to be treated, compared to the patients in the group initially randomized to treatment with prednisolone followed by budesonide. However, these patients treated during the follow-up phase were not excluded from the analysis. Therefore, any bias because of treatment during the study was in favor of placebo-treated patients and thus reducing the observed differences in lung function tests between the groups. However, it should be noted, that all functional abnormalities were small—and even so in patients with stage II disease—may be because of the short duration of disease (<3 months) at the start of the study. Consequently, the treatment effects appear to be modest, too, although statistically significant.

It can be argued that treatment with corticosteroid may result in systemic steroid side effects. As many patients will recover spontaneously, an observation period of 6 to 12 months has been advocated.\(^1\) The risk with this clinical approach is obviously that the subgroup of patients who require treatment will be treated too late. The treatment regimen used in this trial is therefore important, as the long-term maintenance treatment was inhaled medication with budesonide. The pharmacokinetic data speak in favor of a lung uptake high enough to result in a clinically meaningful anti-inflammatory effect. The metabolism of budesonide results rapidly in inactive metabolites; therefore, the risk of systemic side effects can be virtually eliminated. This means that no risk is taken even if some patients would be treated unnecessarily. Despite a favorable benefit-risk ratio, the cost-effectiveness of such a treatment approach needs further evaluations.

This 5-year follow-up study is the first to clearly demonstrate that early treatment of patients with pulmonary stage II sarcoidosis results in an improved functional outcome as measured by lung volumes and DLCO. Patients with stage I disease should be followed up without treatment.

APPENDIX

In addition to the authors, the following investigators and hospitals were members of the Finnish Study Group on Pulmonary Sarcoidosis, and participated in the study: Etelä-Karjala Central Hospital (R. Kauppinen), Etelä-Pohjanmaa Central Hospital (M. Koskenkari, E. Kokko, L. Tuomisto), Hämã Hospital (E. Aalto), Kanta-Häme Central Hospital (M. Järvinen), Keskil-Pohjanmaa Central Hospital (R. Liljqvist, J-H. Slotte), Kiljava Hospital (R. Tammiara, S. Koskinnen), Kuopio University Hospital and Tarina Hospital (R. Majander), Kymenlaakso Central Hospital (M. Havu), Laakso Hospital (A. Ahonen, P. Saarelainen), Lappi Central Hospital (O. Säynäjäkangas), Länsi-Pohja Central Hospital (J. Koniemi), Oulu University Central Hospital (T. Keistinen, O. Rossi), Pietarsaari Hospital, Östland Department (J. Jaakkola), Pohjois-Karjala Central Hospital (E. Perämäki), Sataliina Hospital (V. Tuominen, S. Palohelmo, T. Saarensranta), Savonlinna Central Hospital (K.Venho), Tampere University Central Hospital and Pikonlinna Hospital (M. Nieminen), Turku University Central Hospital and Paimio Hospital (A. Palojoki, P. Laurinen), Vaasa Central Hospital (T. Rinne, L. Lammi).

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