Long-Term Use of Corticosteroid Eye Drops Delays the Spontaneous Remission of Pulmonary Sarcoidosis

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Nara, M., Sasamori, K., Shimura, S., Ogawa, H., Ishigaki-Suzuki, S., Nagaoka, M., Tamada, T., Ichinose, M., Tamura, G. and Hattori, T. Long-Term Use of Corticosteroid Eye Drops Delays the Spontaneous Remission of Pulmonary Sarcoidosis. Tohoku J. Exp. Med., 2004, 202 (4), 275-282 — Topical corticosteroid eye drops are commonly used for ocular sarcoidosis. That systemic absorption of corticosteroids by eye drops may influence the clinical course of sarcoidosis may be speculated because it has been reported that the serum concentration of corticosteroids after drop administration was dose-related. To evaluate the effects of corticosteroid eye drops on the clinical course of patients with stage I pulmonary sarcoidosis, we compared the serum levels of angiotensin converting enzyme (ACE) and bilateral hilar lymphadenopathy (BHL) on chest radiographs of group CS, which is consisted of patients who received topical therapy of betamethasone in the form of eye drops for anterior uveitis, and group CN, which is consisted of patients who did not receive any medications throughout the entire course of the disease. Although the serum ACE level was not significantly different between groups CS and CN at the time of the diagnosis of pulmonary sarcoidosis, the level of serum ACE in group CS was significantly higher than that in group CN 20 months after the topical corticosteroid treatment (24 IU/ml and 16 IU/ml, respectively). Further, the size of BHL on chest radiography in group CS was significantly larger than that in group CN 20 months after the topical treatment (82% and 37% of before control, respectively). These findings suggest the possibility that the topical corticosteroid therapy influenced the clinical course of pulmonary sarcoidosis, inducing some delay in the spontaneous remission in the long-term course. ——— angiotensin converting enzyme; bilateral hilar lymphadenopathy; betamethasone eye drops; spontaneous remission; pulmonary sarcoidosis

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Sarcoidosis is a chronic and systemic disease of unknown etiology that is characterized by non-caseating epithelioid cell granuloma (so called sarcoidosis granuloma). Lungs and thoracic lymph nodes are almost always involved, and extrathoracic involvements, such as erythema nodosum or uveitis, are also seen although their incidences differ among races (Newman et al. 1997). Both bilateral hilar lymphadenopathy (BHL) and anterior uveitis are reported to be more common in Japanese as pulmonary and intraocular manifestations of sarcoidosis, respectively (Ohara et al. 1992).

Generally, systemic or oral corticosteroids are indicated for severe ocular, neurologic, or cardiac sarcoidosis, malignant hypercalcemia and progressive stage II (hilar lymphadenopathy with parenchymal infiltrates), III (parenchymal infiltrates without hilar lymphadenopathy) and IV (fibrosis) pulmonary sarcoidosis (Newman et al. 1997). Other sarcoidosis patients should be observed without therapy because of the potential for spontaneous remission (Silver and Messner 1994; Newman et al. 1997). There have been many reports showing evidence of adverse outcomes in sarcoidosis patients systemically treated with corticosteroids (Young et al. 1970; Israel et al. 1973; Selroos et al. 1974; Harkleroad et al. 1982; Eule et al. 1986; Izumi 1994; Gottlieb et al. 1997; Reich 2002). Meanwhile, topical corticosteroid eye drops are efficient and commonly used for ocular sarcoidosis (Silver and Messner 1994; Newman et al. 1997). It has been reported that the serum concentrations of corticosteroids after single-drop administration to the eyes were dose-related and that high serum concentrations were retained in the sera, resulting in adrenal suppression (Krupin et al. 1976; Baba et al. 1983). Taken together with these findings, we can speculate that systemic absorption of corticosteroids by topical therapy may influence the clinical course of sarcoidosis. To our knowledge, however, there are no studies that show the effect of glucocorticosteroid eye drops on the clinical course of pulmonary sarcoidosis.

In this preliminary report, we examined the effects of such eye drops on serum angiotensin converting enzyme (ACE) and BHL on chest radiograph in patients with stage I pulmonary sarcoidosis and found that the topical corticosteroid therapy appeared to influence the clinical course of pulmonary sarcoidosis, inducing some delay in the spontaneous remission in the long-term usage, as shown in the case of systemic corticosteroid treatment of pulmonary sarcoidosis (Young et al. 1970; Israel et al. 1973; Selroos et al. 1974; Harkleroad et al. 1982; Eule et al. 1986; Izumi 1994; Gottlieb et al. 1997; Reich 2002).

**METHODS**

**Subjects**

During 1990 to 1997, we experienced 128 sarcoidosis patients in Tohoku University Clinic and Hospital. From the complete medical records including cardiac and ophthalmologic examinations and serial examinations of serum ACE and chest radiograph for 2 years or more, 24 patients with stage I pulmonary sarcoidosis were selected for the present study. The diagnosis of pulmonary sarcoidosis was made by the combination of the histology of transbronchial lung biopsy (TBLB) (the presence of non-caseating epithelioid cell granuloma etc.), serum ACE, tuberculin skin test, gallium citrate Ga$^{67}$ scintigraphy, serum lysozyme, computed tomographic (CT) scan, bronchoalveolar lavage (BAL), and clinical features for 4 years or more, excluding pulmonary tuberculosis, hypersensitive pneumonitis, and fungus diseases.

Group CN consisted of patients with stage I pulmonary sarcoidosis who were free of ocular lesions by ophthalmologic examinations and did not receive any medications throughout the entire course of disease (Table 1A). Group CS consisted of patients with stage I pulmonary sarcoidosis who received betamethasone sodium phosphate (BM) solution eye drops for anterior uveitis (Table 1A). There were no significant differences between the two groups in the findings of Ga$^{67}$ scintigram, serum lysozyme, CT, or BAL. BM solution (0.1%) was used in 10 patients of group
CS; 3, 5, and 2 patients received single drops of the steroid solution in both eyes 6, 4, and 3 times a day, respectively. A single drop of 0.1% BM solution contained about 0.05 mg of betamethasone sodium (Baba et al. 1983). All patients in group CS received the topical therapy for 1 year or more and showed some improvement in both their symptoms and ophthalmologic findings (except for one patient).

To determine the early effect of BM solution eye drops on lung histology, we selected 10 patients with stage I and II pulmonary sarcoidosis (group CS-2) who had received eye drops for 4 to 6 weeks until TBLB (Table 1B). BM solution (0.1%) was used in 10 patients of the CS-2 group; 2 and 8 patients received single drops of the steroid solution in both eyes 6 and 4 times a day, respectively. As the controls, there were 30 patients with I and II pulmonary sarcoidosis (group CN-2) who had received no treatment for at least 4 to 6 weeks until TBLB. The histological findings of biopsy samples from group CS-2 and CN-2 were compared.

**Serum angiotensin-converting enzyme**

Serum angiotensin-converting enzyme (ACE) activity from each patient was measured an assay using the colorimetric method as described previously (Kasahara and Ashihara 1981) at intervals of 1 to 2 months for 2 years or more. A value of 21.4 U/ml or greater was ascertained to be elevated.

**Chest radiograph**

Chest radiograph was obtained from each patient with the same machine (FCR5000, Fuji film medical, Tokyo) under the same exposure conditions and printed with the same type of film.

![Graph showing the effect of topical treatment of betamethasone on the serum ACE in the pulmonary sarcoidosis patients.](image-url)

Fig. 1. The effect of topical treatment of betamethasone on the serum ACE in the pulmonary sarcoidosis patients. The serum ACE level of the non-therapeutic (CN) group (15.5±2.4 IU/ml, n=14) was significantly lower than that of the topical therapeutic (CS) group (23.8±4.2 IU/ml, n=10) 20 months after diagnosis, at which time these levels were not different (24.9±4.0 IU/ml and 26.2±2.3 IU/ml, respectively, p=0.037) at the time of diagnosis. *p<0.05.

●, Topical therapy (CS) group; ○, Non-therapy (CN) group.
at intervals of 1 to 2 months for 2 years or more. The size of BHL was estimated by weighing cutouts of the drawings of the chest radiographs. The measurement of BHL on chest radiographs was performed without knowledge of the case number by 2 chest physicians and the mean value was used for data analysis.

Transbronchial lung biopsy

Under topical anesthesia of lidocaine hydrochloride, transbronchial lung biopsy (TBLB) was performed. Three to 5 biopsy samples were obtained from the right lung of each patient.

Statistics

Statistical analysis was performed using the unpaired t-test (histologically positive rate of non-caseating granuloma), Mann-Whitney’s U-test (age, serum ACE levels, and %BHL) and Fischer’s exact probability test (sex). A p-value <0.05 was considered significant. Data were expressed as mean±S.E.

RESULTS

As shown in Table 1A, the patients in the CN group were older than those in the CS group although not significantly (p=0.11), and both the sex and race distribution were similar in the two groups.

Serum ACE levels

At the time of diagnosis of pulmonary sarcoidosis, there were no significant differences in the serum ACE levels between the CN and CS groups (24.9±4.0 IU/ml and 26.2±2.3 IU/ml, respectively). The serum ACE level in each patient showed a gradual decrease for 2 years or more. However, the serum ACE levels from the CN group showed greater decreases than those from the CS group, and the ACE levels from the CN group were significantly lower than those from the CS group 20 months after the diagnosis or topical treatment (15.5±2.4 and 23.8±4.2 IU/ml, respectively, p=0.037) (Fig. 1).

![Fig. 2. The effect of topical treatment of betamethasone on the size of BHL on chest radiograph in the pulmonary sarcoidosis patients. The size of BHL was expressed as a percentage of that at the time of diagnosis. The BHL on chest radiography of the non-therapeutic (CN) group was significantly diminished in size 20 months after diagnosis compared to that of the topical therapeutic (CS) group (36.9±11.9% and 82.2±17.7% of before control, respectively, mean±S.E., p=0.029). *p<0.05.

●, Topical therapy (CS) group; ○, Non-therapy (CN) group.]
**BHL size on chest radiograph**

Coincident with the changes in the serum ACE level, the BHL sizes showed a gradual decrease in each patient, and those from the CN group showed a greater decrease than those from the CS group. There were significant differences in the BHL sizes between the CN and CS groups 20 months after the diagnosis or topical treatment (36.9±11.9 vs. 82.2±17.7% of before control, respectively, \( p=0.029 \)) (Fig. 2).

**Non-caseating granuloma by TBLB**

When one or more biopsy samples from each patient contained a non-caseating granuloma, it was determined to be histologically positive. Although it did not reach statistical significance, the positive rate of the CS-2 group had a tendency to be lower than that of the CN-2 group (50.0 and 73.3%, respectively, \( p=0.31 \)).

**DISCUSSION**

The results of the present study of the serial serum ACE and chest radiograph BHL-size measurements suggest that long-term BM solution eye drops influence the clinical course of pulmonary sarcoidosis, including some delay in the spontaneous remission.

It may be difficult to assess the effects of the corticosteroids on pulmonary sarcoidosis since sarcoidosis tends to follow a benign clinical course in the majority of patients (Newman et al. 1997). The serum ACE activity is a sensitive index for evaluating the clinical course of sarcoidosis including spontaneous remission (DeRemee and Rohrbach 1980; Rohatgi et al. 1981), and the size of BHL on chest radiograph has been shown to change in parallel with the activity of stage I pulmonary sarcoidosis that shows spontaneous remission (Newman et al. 1997; The American Thoracic Society et al. 1999). Chest CT examination, which would enable to accurate measurement, was not used for the present study because of the substantial radiation exposure.

The severity of the two groups at the time of diagnosis in the present study was almost the same since both ACE levels and BHL sizes were not significantly different between the two groups. The corticosteroid eye drops delayed the improvement or decrease of both the ACE level and the size of BHL 20 months after the treatment. It has been reported that the serum concentrations of corticosteroids after single-drop administration to the eyes were dose-related and that high serum concentrations were retained in the sera (Krupin et al. 1976; Baba et al. 1983), although our report lacks data of the serum concentrations because it was a retrospective study. The doses of corticosteroids by eye drops in the CS group of the present study were similar to those reported to effect adrenal function through systemic absorption with long-term usage (Baba et al. 1983). Taken together with these reports, we can speculate that systemic absorption of topical corticosteroid therapy adversely affects the course of pulmonary sarcoidosis.

We have assumed that the course of pulmonary sarcoidosis is uninfluenced by the presence of uveitis since we could not find any reports concerning the adverse effect of uveitis on the clinical course. Additionally, advanced age is known to be one of the adverse prognostic factors of sarcoidosis (The American Thoracic Society et al. 1999). As shown in Table 1A, the patients in the CN group were older than those in the CS group although not significantly. Therefore, the difference between the two groups in both serum ACE and the size of BHL 20 months after the topical treatment would have been more prominent if the ages between the two groups had been matched.

The adverse effects of corticosteroids on the course of sarcoidosis have been reported by several investigators (Young et al. 1970; Israel et al. 1973; Selroos et al. 1974; Harkleroad et al. 1982; Eule et al. 1986; Izumi 1994; Gottlieb et al. 1997; Reich 2002). For example, Eule et al. (1986) reported an evaluation of the long-term influence of oral corticosteroid therapy on the natural course of asymptomatic pulmonary sarcoidosis. They reported that relapse occurred in 22% of the patients in the treated group and concluded
that corticosteroid therapy did not have a real influence on the long-term course of sarcoidosis regardless of the radiographic stage (Euel et al. 1986). Further, Izumi (1994) reported that, at 10 years, the outcome favored the untreated group: 24% in the group treated orally with corticosteroids vs. 8% in the untreated group had persistent radiographic abnormalities. Also, clinical and radiographic deterioration was observed in 5% in the treated group – in one instance severe enough to require continuous oxygen therapy – but in no patients of the untreated group. Our results are

<table>
<thead>
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<th>TABLE 1. Patients’ demographics</th>
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A

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<th></th>
<th>CN Group¹</th>
<th>CS Group²</th>
<th>p-value</th>
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<tr>
<td>No. of patients</td>
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<td>10</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>9 (64%)</td>
<td>5 (50%)</td>
<td>p=0.68</td>
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<td>Female</td>
<td>5 (36%)</td>
<td>5 (50%)</td>
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<tr>
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<td></td>
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<tr>
<td>Japanese</td>
<td>14 (100%)</td>
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<tr>
<td>Age (years±S.E.)</td>
<td>50.3±18.6</td>
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<td>Range</td>
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¹The CN group consisted of patients with stage I pulmonary sarcoidosis who did not receive any medications throughout the entire course of the disease.

²The CS group consisted of patients with stage I pulmonary sarcoidosis who received topical therapy of betamethasone sodium phosphate solution eye drops for anterior uveitis.

B

<table>
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<tr>
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<th>CN-2 Group¹</th>
<th>CS-2 Group²</th>
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<tr>
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<td>6 (60%)</td>
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<tr>
<td>Female</td>
<td>12 (40%)</td>
<td>4 (40%)</td>
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<tr>
<td>Race</td>
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<tr>
<td>Japanese</td>
<td>30 (100%)</td>
<td>10 (100%)</td>
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<tr>
<td>Age (years±S.E.)</td>
<td>41.0±2.7</td>
<td>32.9±6.5</td>
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</table>

¹The CN-2 group consisted of 30 patients with stage I and II pulmonary sarcoidosis who had received no treatment for at least 4 to 6 weeks until TBLB.

²The CS-2 group consisted of 10 patients with stage I and II pulmonary sarcoidosis who had received BM solution eye drops for 4 to 6 weeks until TBLB.
mostly compatible with these results in spite of the fact that the treatment of corticosteroids was only with topical eye drops.

Serial measurement of serum ACE or chest radiograph failed to show an early effect of decreased sarcoidal inflammation by the steroid eye drops. Meanwhile, after 4 to 6 weeks of topical treatment, the histologically positive rates of non-caseating granuloma in the TBLB biopsy samples from the CS group had a tendency to be lower (50.0%) compared with those from the CN group (73.3%), although the difference was not statistically significant. Treatment with oral corticosteroids is known to prevent short-term deterioration of chest roentgenographic findings and lung functions (du Bois 1994; Hunninghake et al. 1994; Gibson et al. 1996; The American Thoracic Society et al. 1999). Therefore, the finding that the topical administration (eye drops) of corticosteroids had a tendency to reduce the non-caseating granulomas (sarcoidosis granuloma) in lung tissue is consistent with the known effects of oral corticosteroids in suppressing the acute consequences of widespread pulmonary granuloma (Gibson et al. 1996).

In conclusion, topical administration of corticosteroids by eye drops influences the clinical course of pulmonary sarcoidosis through the systemic absorption, producing some delay in the spontaneous remission. These findings should be confirmed by a prospective randomized double-blind study with a larger number of patients in the future.

Acknowledgments

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References


