Efficacy of short-term prednisolone treatment in patients with chronic eosinophilic pneumonia

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ABSTRACT In patients with chronic eosinophilic pneumonia (CEP), dramatic improvements are seen in response to corticosteroid therapy; however, relapse is common after treatment has ceased. The optimal duration of corticosteroid therapy remains unclear.

In a randomised, open-label, parallel group study, eligible patients with CEP received oral prednisolone for either 3 months (3-month group) or 6 months (6-month group), followed by 2 years observation. All patients were treated with an initial dose of prednisolone of 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$, which was then tapered and discontinued at either 3 or 6 months. The primary end-point was relapse during the follow-up period.

In the final analysis, there were 23 patients in the 3-month group and 21 patients in the 6-month group. All patients showed a good response to prednisolone treatment. There were 12 (52.1%) relapses in the 3-month group and 13 (61.9%) relapses in the 6-month group. No significant difference was found in the cumulative rate of relapse (p=0.56). All relapse cases showed improvement upon resumption of prednisolone treatment.

No difference was observed in the rate of relapse between the 3- and 6-month prednisolone treatment groups for patients with CEP.

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Introduction

Chronic eosinophilic pneumonia (CEP) is an idiopathic pulmonary disorder characterised by marked accumulation of eosinophils in the lungs, which was first described in 1969 [1, 2]. CEP predominantly occurs in middle-aged women, and common symptoms include cough, fever, dyspnoea, fatigue and malaise [3, 4]. In the peripheral lungs, the imaging features of CEP consist of multiple patchy infiltrations with ill-defined margins [5–12], and spontaneous migration of these infiltrates occurs in approximately 25% of patients [13]. Diagnosis relies on clinical signs, typical imaging findings and blood and/or alveolar eosinophilia once other aetiological diagnoses have been excluded. As approximately half of CEP patients have atopic diseases, such as bronchial asthma, CEP is considered to be associated with allergic factors [3, 13, 14].

Systemic corticosteroids are the mainstay of treatment in CEP [15–17]. Oral corticosteroid treatment, such as 0.5–1.0 $mg \cdot kg^{-1} \cdot day^{-1}$ of prednisolone, leads to a dramatic improvement in both clinical and radiological symptoms [3, 5]; however, the optimal duration of treatment has not yet been determined. In spite of an initial favourable response to corticosteroid treatment, symptomatic and radiographic relapses occur in ~30–50% of patients once steroid therapy is tapered or discontinued [16, 18, 19]. MARCHAND *et al.* [16] recommend an initial oral corticosteroid therapy duration of at least 6 months based on the high rate of relapse they found in patients initially treated for <6 months; however, this was a retrospective analysis, and the initial dose and tapering schedules for corticosteroid therapy were not consistent. Thus, a prospective therapeutic study is required to clarify the optimum duration of corticosteroid treatment for patients with CEP.

Although patients with CEP often experience relapse, they usually have a favourable response upon resumption of corticosteroid treatment, and a good overall prognosis [16, 19]. In a clinical setting, it is important to avoid the serious adverse effects of long-term corticosteroid therapy to maintain patient quality of life. Given the dramatic response to corticosteroid treatment that is observed, and the good prognosis for patients with CEP, short-term systemic corticosteroid administration (<6 months) may be sufficient. In the present study, we prospectively compared the efficacy and safety of short-term corticosteroid treatment (oral prednisolone for 3 months) with long-term treatment (oral prednisolone for 6 months) in patients with CEP.

Materials and methods

Patient selection

Patients were prospectively enrolled at the Hamamatsu University Hospital (Hamamatsu, Japan) and related hospitals. Patients (16–79 years of age) were eligible if they had recently received a diagnosis of CEP that met all of the following inclusion criteria: clinical symptoms suggestive of CEP (*e.g.* fever, cough or dyspnoea on exertion) lasting for >1 month; infiltrative shadows on chest radiographs; eosinophilia in bronchoalveolar lavage (BAL) fluid and/or evident eosinophilic infiltration in transbronchial lung biopsies (TBLB); and exclusion of infection. Patients were excluded from the study if one or more of the following criteria applied: use of ≥10 mg of prednisolone per day; use of immunosuppressants; and presence of a serious comorbidity (*e.g.* diabetes mellitus, uncontrolled hypertension, gastrointestinal ulcers with bleeding, glaucoma, liver dysfunction and renal dysfunction).

The study protocol was approved by the Ethical Committee of the Hamamatsu University School of Medicine, Hamamatsu (approval number: Hamamatsu 18–67) and each patient provided written informed consent. This study is registered at clinicaltrials.gov (identifier: NCT00632554).

Study design

This was a multicentre, randomised, open-label, parallel group study. Patients were randomly assigned in a 1:1 ratio into two groups. 1) A 3-month group in which patients received 0.5 $mg \cdot kg^{-1}$ prednisolone once daily, and in which prednisolone was tapered by ~20% every 2 weeks and discontinued after 3 months; or 2) a 6-month group in which patients received 0.5 $mg \cdot kg^{-1}$ prednisolone once daily, and in which prednisolone was tapered by ~20% every 2 weeks for 2 months, and thereafter by ~20% every 3 weeks, and discontinued after a total of 6 months. All patients were observed for 2 years after completion of each treatment.

Relapse rate as the primary outcome was used to determine the sample size based on the assumption of a relapse rate of 30% in both groups. A sample size of 58 was required to detect the 30% difference in relapse rate between two groups at a 0.05 significance level with 80% power.

End-points and follow-up

The primary end-point was relapse during treatment or follow-up. The secondary end-points were the response to initial treatment and the safety of each treatment. The patients underwent blood tests (including blood sugar test) and chest radiographs at least once a month during the treatment period, and once every 3 months during the observation period, to evaluate responses to treatment and relapse.

Response to treatment was defined as an improvement in subjective symptoms, infiltrative shadows on chest radiographs and/or high-resolution computed tomography (HRCT) images, and blood or BAL eosinophilia. Relapse was defined as two or more of the following: 1) a recurrence of subjective symptoms; 2) an increase in infiltrative shadows on chest radiographs and/or HRCT images; and 3) a recurrence of blood or BAL eosinophilia. In relapse cases, infections were excluded if there was no clinical (*e.g.* grossly purulent sputum was absent and patients were resistant to antibiotic therapy) or microbiological evidence for infection. Safety was assessed by means of clinical and laboratory evaluation at study visits and the recording of adverse events.

Data collection

After screening, baseline data were collected on patient demographics (*e.g.* sex, age, smoking history, past medical history and complications), laboratory analyses (blood cell counts, C-reactive protein (CRP), IgE and arterial blood gas analysis), pulmonary function tests (forced vital capacity and forced expiratory volume in 1 s), chest radiography and HRCT, and bronchoscopic tests (BAL and TBLB). Chest radiographs were assessed by at least one or more pulmonologist with >10 years' experience.

BAL

BAL was performed as previously described [20, 21]. Briefly, bronchial trees were instilled three times with 50 mL normal saline and fluid was removed each time by gentle suction. Supernatants were separated from cell pellets by centrifugation at 800×*g* for 5 min at 4°C. Slides were prepared by cytocentrifugation and Wright–Giemsa staining, and a differential count of 500 cells was performed.

HRCT findings

HRCT of the lungs to detect radiographic abnormalities was performed with a slice thickness of 1.0 mm or 1.5 mm, and images were reconstructed using a high spatial frequency algorithm. HRCT images were reviewed for the presence of each of the following signs: consolidation, ground-glass opacities, reticulation and pleural effusion according to the Fleischner criteria with slight modifications [22]. Consolidation was defined as a homogeneous increase in pulmonary parenchymal attenuation that obscured the underlying vessels. Ground-glass opacities were defined as an increased level of hazy attenuation of the lungs that did not obscure the underlying vessels. Reticulation was defined as a collection of innumerable small linear opacities that, by summation, produced a net-like appearance. All computed tomography findings were recorded as present or absent. The HRCT images were randomised and reviewed independently by two pulmonologists with >10 years' experience (Y. Oyama and T. Fujisawa).

Statistical analysis

Comparisons of binary data between the two groups were performed using Fisher's exact test and continuous data were compared using the Mann–Whitney U-test. The cumulative relapse rate was calculated using the Kaplan–Meier method and the log-rank test was used to compare the relapse rate between the two groups. The Cox proportional hazards model was used for univariate analysis. All data are expressed as the median (interquartile range). All statistical analyses were performed using JMP version 9.0 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was regarded as statistically significant.

Results

Clinical features and laboratory findings

A total of 55 patients underwent randomisation (fig. 1). 11 of these patients were excluded from the study because of a lack of data (n=8), diagnosis with another disease (n=2) or withdrawal of consent (n=1). Therefore, 44 patients (23 in the 3-month group and 21 in the 6-month group) were subject to analysis.

The baseline characteristics of patients assigned to each treatment group are summarised in table 1. Clinical characteristics were similar for both groups in terms of symptoms, sex, age and smoking history. More than half of patients in both groups had bronchial asthma; patients in both groups had similar levels of peripheral blood eosinophilia and a high percentage of eosinophils in the cellular component of BAL fluid. There were no significant differences between the groups in laboratory findings or the results of pulmonary function tests (table 2). According to arterial blood gas analysis, no patients had respiratory failure except one patient in the 6-month group (arterial oxygen tension 58 Torr). The frequency of signs identified *via* HRCT is summarised in table 2. Consolidation and ground-glass opacities were the most frequently identified signs for both groups, and there were no significant differences in HRCT findings between groups. The area involved and area of distribution were also not different between groups. TBLB was performed in 42 patients upon initial diagnosis of CEP. In 33 patients in whom TBLB could be performed, the specimens showed eosinophilic infiltration to the alveoli and bronchioles. Nine patients did

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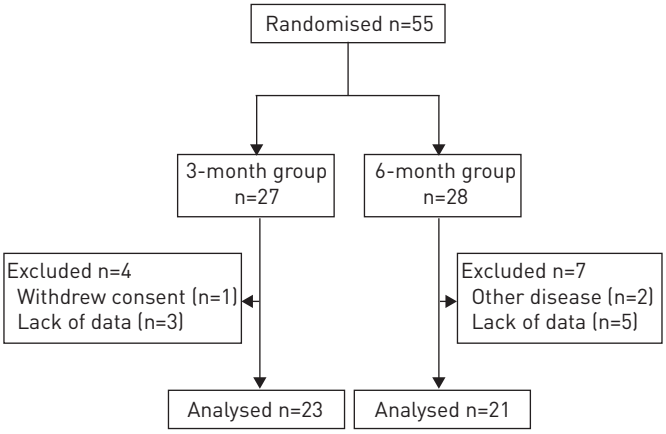

FIGURE 1 Study flow chart.

TABLE 1 Patient characteristics

	3-month group	6-month group	p-value
Patients n	23	21	
Age years	65 (49–71)	59.5 (56–70)	0.34
Male/female n	6/17	9/12	0.87
Current/former/never-smoker n	1/9/13	0/8/13	1
Prior asthma	16 (69.6)	11 (52.4)	0.35
Symptoms			
Cough	13 (56.5)	16 (76.2)	0.21
Sputum	7 (30.4)	4 (19)	0.49
Fever	9 (39.1)	4 (19)	0.19
Dyspnoea	7 (30.4)	5 (23.8)	0.74
General fatigue	3 (13)	0 (0)	0.23

Data are presented as median (interquartile range) or n (%), unless otherwise stated.

not have conspicuous eosinophilic infiltration in the lung specimens, but had high percentages of eosinophils in BAL fluid.

Efficacy and follow-up

In both groups, all patients showed a good response to prednisolone therapy (table 3). Relapse was observed in 12 (52.1%) cases in the 3-month group and in 13 (61.9%) cases in the 6-month group. There was no significant difference between the 3-month group and 6-month group in the primary end-point of relapse ($p=0.56$) (table 3). In addition, there was no significant difference in the cumulative relapse rate curve between the two groups ($p=0.39$) (fig. 2). The median time to relapse was 182 days in the 3-month group and 211 days in the 6-month group (table 3), with no statistical difference between groups. Chest HRCT was routinely repeated at the end of the treatment period and at the time of relapse in patients who relapsed. The abnormal findings of HRCT images at CEP diagnosis were improved at the end of treatment period. The major findings of HRCT in the patients who relapsed were consolidation and ground-glass opacities, which were consistent with the findings at initial diagnosis. There were no differences in HRCT findings of the patients with relapse between the groups (data not shown). All patients who relapsed showed improvement upon resumption of prednisolone (≤ 0.5 mg·kg^{-1}·day^{-1}), although retreatment protocol was not defined in this study. Eight patients (3-month group: n=2; 6-month group: n=6) presented two periods of relapse during the follow-up period, and they had good response to prednisolone as initial episodes.

The factors contributing to CEP relapse were analysed using a univariate Cox proportional hazards model. The results are shown in table 4. None of the factors analysed, including treatment period, were significantly associated with CEP relapse.

Safety

Adverse events are shown in table 5. In the 3-month group, two cases of infection, one case of hyperglycaemia and one case of steroid psychosis were observed, while in the 6-month group there were two

TABLE 2 Results of laboratory, bronchoalveolar lavage and high-resolution computed tomography (HRCT) analyses

	3-month group	6-month group	p-value
Laboratory			
CRP mg·dL^{-1}	2.0 (0.3–5)	2.6 (0.7–5.1)	0.56
WBC cells·mm^{-3}	8400 (6700–9500)	8000 (6400–11100)	0.81
Eosinophils cells·mm^{-3}	2070 (1140–2970)	1400 (810–4180)	0.65
IgE IU·mL^{-1}	366.6 (208–868)	429.8 (336–737)	0.56
P_{aO_2} in room air Torr	83.2 (79.5–90.4)	82.1 (72.7–87.9)	0.49
Pulmonary function			
FVC % pred	82.8 (76.3–99.2)	84.1 (70.6–90.2)	0.74
FEV_1 % pred	88.9 (78.0–98.7)	75.6 (62.2–96.5)	0.22
FEV_1/FVC %	80.3 (75.4–90)	77.6 (61.3–81.3)	0.17
Bronchoalveolar lavage			
TCC ×10^{5}cells·mL^{-1} BALF	2.4 (1.3–4.6)	3.2 (1.7–4.8)	0.33
Macrophages %	48.0 (24.0–73.1)	35.0 (20.4–55)	0.16
Lymphocytes %	6.6 (3.0–13)	10.0 (5.2–17)	0.20
Neutrophils %	2.0 (0.5–6)	1.0 (0.5–2)	0.53
Eosinophils %	33.0 (15.0–57)	35.0 (22.0–58)	0.69
CD4/CD8 ratio	1.5 (1.0–2.4)	1.3 (0.7–1.5)	0.07
HRCT			
Consolidation	16 (69.6)	20 (90.9)	0.13
Ground-glass opacities	15 (65.2)	16 (72.7)	0.75
Reticulation	4 (17.4)	1 (4.5)	0.35
Pleural effusion	1 (4.3)	1 (4.5)	1

Data are presented as median (interquartile range) or n (%), unless otherwise stated. CRP: C-reactive protein; WBC: white blood cell; P_{aO_2}: arterial oxygen tension; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TCC: total cell count; BALF: bronchoalveolar lavage fluid.

cases of infection, one case of hyperglycaemia and one case of bone fracture. None of the patients had a fatal adverse event or discontinued prednisolone treatment. No deaths were reported during the study period.

Discussion

In the present study, we prospectively compared the efficacy and safety of 3- and 6-month prednisolone treatment for patients with CEP. There was no significant difference in the cumulative relapse rate between the two groups during the study period, which is the major finding in this study. All patients, from both groups, responded well to initial prednisolone treatment and those who relapsed improved upon prednisolone resumption. In addition, adverse effects profiles were similar for both treatments, and none of the patients discontinued prednisolone treatment. Collectively, these data demonstrate that the efficacy of 3 months of prednisolone treatment may be equivalent to that of 6 months of treatment for patients with CEP, particularly in relation to relapse.

To our knowledge, this is the first report of a randomised, prospective, comparative study to compare the efficacy of 3 and 6 months of prednisolone treatment in patients with CEP. In the present study, there was no difference in the rate of relapse between 3 or 6 months of prednisolone treatment. The response to systemic corticosteroid therapy is dramatic, and the prognosis for CEP patients is generally good under this treatment [16, 19]. Thus, the main concerns regarding practise in relation to relapse is in determining when treatment should be tapered or discontinued. Some retrospective studies have reported a high frequency of

TABLE 3 Patient outcomes

	3-month group	6-month group	p-value
Response to initial treatment	23 (100)	21 (100)	1
Relapse	12 (52.1)	13 (61.9)	0.56
Time to relapse days	182 (156–224)	211 (152–282)	0.73

Data are presented as n (%) or median (interquartile range), unless otherwise stated.

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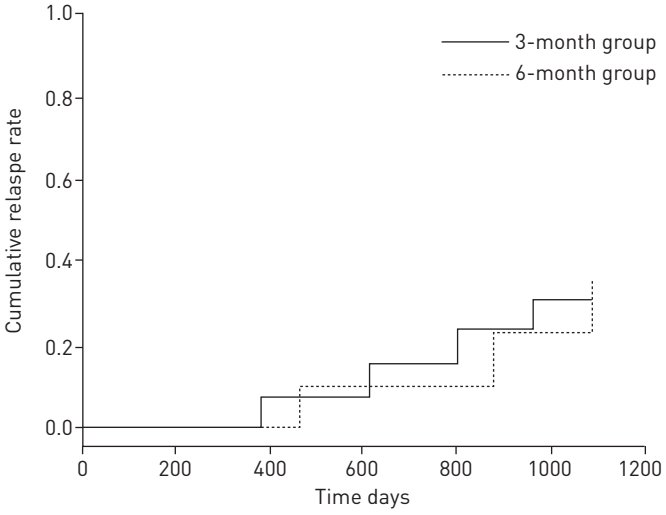

FIGURE 2 Cumulative relapse rate curves for the 3- and 6-month groups. Chronic eosinophilic pneumonia relapse occurred in 12 (52.1%) patients in the 3-month group and 13 (61.9%) patients in the 6-month group. There was no statistical difference in the cumulative relapse rate between the two groups (p=0.39).

TABLE 4 Factors associated with chronic eosinophilic pneumonia relapse

	Hazard ratio (95% CI)	p-value[#]
Age years	1.024 (0.978–1.072)	0.318
Female *versus* male	1.445 (0.547–3.82)	0.458
Smoking status *versus* never-smoker	1.052 (0.41–2.698)	0.916
Prior asthma	1.075 (0.394–2.929)	0.888
FVC %	0.996 (0.96–1.033)	0.819
FEV_1	1.014 (0.981–1.048)	0.406
CRP	1.025 (0.955–1.1)	0.501
Eosinophils	1 (0.999–1)	0.261
IgE	0.999 (0.998–1)	0.261
BAL eosinophils %	1.004 (0.983–1.027)	0.689
3-month *versus* 6-month treatment	1.535 (0.572–4.121)	0.395

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; CRP: C-reactive protein; BAL: bronchoalveolar lavage. [#]: univariate Cox proportional hazards model.

TABLE 5 Adverse events associated with treatment

	3-month group	6-month group
Infection	2	2
Hyperglycaemia	1	1
Osteoporosis/bone fracture	0	1
Psychosis	1	0

Data are presented as n.

relapse in CEP patients treated with oral corticosteroids for too short a period (*e.g.* <6 months) [5, 16]. Although longer oral corticosteroid therapy may provide protection from further relapse, to date, no prospective comparative studies have been conducted to determine the optimal length of corticosteroid treatment. In the present study we have shown that the rate of relapse was equal for 3 and 6 months of prednisolone treatment. In addition, the adverse effects profiles for both treatments were similar, and all patients who relapsed improved upon prednisolone resumption. These findings suggest that the efficacy of 3 months of corticosteroid treatment is equivalent to that of 6 months of treatment. Given the risks of long-term prednisolone treatment, 3 months of treatment may represent a more suitable therapeutic option for patients with CEP.

It is important to consider optimal dose and period of drug administration for the treatment of any diseases. In general, when the efficacy of short-term treatment is as equivalent as that of long-term treatment, short-term treatment is preferred over long-term treatment in the view of better adherence to treatment and reduction of adverse effects. In the present study, an initial dose of 0.5 $mg \cdot kg^{-1}$ of prednisolone daily provide favourable response in all the patients with CEP, which indicates the dose is appropriate for the initial treatment of CEP. In terms of treatment period, 3 months of prednisolone treatment was equal to 6 months of prednisolone treatment in response to treatment, rate of relapse and frequency of adverse effects. In addition, all patients who relapsed showed improvement upon resumption of prednisolone and none of the patients died during the study period. These findings can lead us to conclude that 3 months of (short-term) prednisolone treatment at an initial dose of 0.5 $mg \cdot kg^{-1}day^{-1}$ is a feasible therapeutic option for the patients with CEP.

One of the major concerns in CEP is to find any predictive factors for relapse of CEP at the time of initial diagnosis. In this study, we have attempted to determine whether CEP relapse is predictable at the time of initial diagnosis. Using a univariate Cox proportional hazards model, we analysed the factors contributing to CEP relapse; however, none of factors examined, including laboratory results, pulmonary function test results and BAL results, were significantly associated with relapse. To date, no investigation of predictive factors in CEP relapse has been published. In this context, our findings indicate that relapse is difficult to predict at initial diagnosis.

This study has certain limitations. First, the study population is relatively small for the collection of information on important end-points such as relapse. In this study, although 55 patients initially underwent randomisation, 11 patients were excluded from the final analysis due to various reasons. Thus, the statistical power of the study may not allow a minor difference in relapse rate to be detected between the two groups. Further investigations are needed to confirm the difference. Secondly, the study duration may not have been long enough to evaluate the long-term consequences of CEP. Finally, this was an open-label, not a double-blind, study. Given the rarity of this disease, however, it is unlikely that a prospective, randomised, double-blind trial with a large number of patients and a longer observation period will be conducted in the near future. Despite these limitations, this is the first randomised, open-label, parallel-group study to compare the efficacy of short-term corticosteroid treatment (3 months) with long-term treatment (6 months) for patients with CEP, and to provide significant information on CEP treatment.

In conclusion, this study provides evidence that no difference was observed in the rate of relapse between 3 and 6 months of prednisolone treatment for patients with CEP. Our results indicate that 3 months of prednisolone treatment is a more useful therapeutic option for patients with CEP in terms of reducing the potential for adverse effects relating to long-term corticosteroid treatment.

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