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Clinical Characteristics and Corticosteroid Treatment of Acute Eosinophilic Pneumonia

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Abstract

The clinical characteristics and optimal duration of corticosteroid treatment for acute eosinophilic pneumonia (AEP) have not been fully evaluated. This was a retrospective study of prospectively collected data of 137 patients with AEP treated with standardized protocol to clarify the clinical characteristics and to compare the efficacies of two weeks vs. four weeks of corticosteroid treatment for AEP. The majority of the patients altered their smoking habits within a median of 17 (interquartile range, 13 – 26) days prior to development of AEP. Eighty (58%) patients presented with acute respiratory failure. A total of 127 (92%) patients were treated with corticosteroid: for four weeks in 42 and for two weeks in 85. Major symptoms were resolved in three days and severity of respiratory failure was inversely correlated with clinical outcomes. After adjusting for differences in baseline characteristics between the groups, the differences in adjusted means (95% CI) for resolution of dyspnea and disappearance of all symptoms were 0.57 (-0.71 – 1.86) days and -0.04 (-1.91 – 1.83) days, respectively. The difference in adjusted proportion of resolution of radiological abnormalities was 6.92% (-8.19 – 22.02). In conclusion, the duration of corticosteroid treatment could be shortened to two weeks even in patients with respiratory failure.

Key words: pulmonary eosinophilia; acute disease, smoking, respiratory insufficiency, treatment outcome

Introduction

Acute eosinophilic pneumonia (AEP) is an acute febrile illness with severe hypoxemia, diffuse pulmonary infiltrates, and an increase in bronchoalveolar lavage (BAL) eosinophils and no evidence of infection or previous atopic illness [1]. Less than 100 cases with AEP have been reported to date [2], with the largest series including only 33 patients [3]. Therefore, clinical characteristics, especially the course of resolution of symptoms and resolution of radiographic abnormalities, have not yet been fully evaluated.

AEP is also characterized by rapid response to corticosteroids with few relapses and improvement of radiographic abnormalities without fibrosis [1, 4]. However, the proposed corticosteroid regimen varies greatly with a wide range of recommended dosages. The optimal duration of corticosteroid treatment is also uncertain, and there have been no controlled trials to guide clinicians in their use of corticosteroids. In addition, there are several reports of patients improving spontaneously without corticosteroid treatment [3, 5, 6].

A retrospective analysis of clinical data from 137 cases of AEP was performed to clarify clinical characteristics including resolution of associated symptoms and resolution of radiological abnormalities after corticosteroid treatment. In addition, the efficacy and safety of a short course (two weeks) of corticosteroid treatment was compared to a long course (four weeks) of treatment.

Materials and Methods

The medical records of all consecutive patients who were diagnosed with AEP at the Armed Forces Capital Hospital, an 874-bed referral military hospital in Gyeonggi province, South Korea, between May 2007 and October 2010 were retrospectively reviewed. The study was approved by the institutional review board of the Armed Forces Capital Hospital to review and publish information from the patients' records. The requirement for informed consent was waived because of the retrospective nature of the study.

Study Subjects

All consecutive patients who were suspected to have AEP with a febrile illness with respiratory symptoms and diffuse pulmonary infiltrates were prospectively registered for the study period. Definite diagnosis of AEP was based on a modification of criteria proposed by Philit et al. [5] as followed: 1) acute onset of febrile respiratory manifestations <1 month in duration; 2) bilateral diffuse infiltrates on chest radiograph; 3) >25% eosinophils on BAL or eosinophilic pneumonia on lung biopsy; 4) absence of known causes of pulmonary eosinophilia, including drugs, toxins, and infections. Unlike Philit et al.[5], patients with or without hypoxemia were included to identify all possible cased of AEP [7].

Baseline Data, Treatment Protocol, and Measurements During Follow-up

The following data were recorded at the time of presentation: general characteristics of the patients including demographic data, detailed smoking history including the duration of smoking, symptoms and signs, and laboratory measurements including arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (PF ratio). In all instances, patients were interviewed about exposures that may result in pulmonary eosinophilia and

drug histories were reviewed. In addition, patients underwent evaluation for potential parasite infection with history of eating and serologic test. Chest radiograph and high-resolution computed tomography (HRCT) of the lungs were performed for all patients. Bronchoscopy with BAL was carried out at the time of presentation based on the constellation of clinical and radiological findings. BAL was done using the standard techniques as previously described [8]. Once wedged, a 30 mL of normal saline at room temperature was instilled through the bronchoscope and then was retrieved using a negative suction pressure adjusted to avoid visible airway collapse (less than 100 mm Hg). The procedure was then repeated until a total of at least 120 mL was instilled. The percentages of eosinophils in BAL fluid were determined on cytocentrifuged slides using standard criteria.

After confirmative diagnosis of AEP was made, corticosteroid treatment was initiated according to a standardized protocol. The attending physician chose a regimen based on the presence of respiratory failure defined as PF ratio $\leq$300 and/or tachypnea (respiration rate >30 /min). When the patient had respiratory failure, 60mg of mehyprednisolone was administered intravenously every six hours for three days and then changed to 30mg oral prednisolone twice a day (Table 1). When the patient had no respiratory failure, 30mg oral prednisolone twice a day was administered (Table 1). When the oxygenation was not severe (PF ratio >350) and dyspnea symptoms were mild, corticosteroids were not administered. From May 2007 to May 2008, four-week corticosteroid treatments were administered. However, in June 2008, the treatment duration was reduced to two weeks because of potential side effects of long-term corticosteroid use. From June 2008 to March 2009, both four-week and two-week treatments of corticosteroids were administered. From April 2009 to October 2010, only two-week corticosteroid treatments were administered. These regimens of corticosteroid treatment are described in Table 1.

During the treatment, clinical symptoms and signs were evaluated daily by attending physician. Moreover, laboratory tests and chest radiographs were performed weekly. Follow-up HRCT was performed 14 days after the initiation of corticosteroid treatment. The time to resolution of individual vital signs and clinical status abnormalities was defined as the first day that the vital sign or clinical variable was stable [9].

Evaluation of Radiological Findings

Chest radiographs were reviewed for the presence of pulmonary infiltrates and pleural fluids. HRCT images were also reviewed for the presence of each of the following signs: ground glass opacity, air-space consolidation, nodular opacity, interlobular septal thickening, thickening of bronchovascular bundle, and pleural effusion [10]. During follow-up, clearances of pulmonary infiltrates and pleural effusion defined as the absence of any radiographic sign were established. Radiological findings were retrospectively analyzed by two of the authors (Rhee, CK and Yim, NY). Differences in observed findings were resolved by consensus.

Data Analysis

Because the majority of the data did not follow a normal distribution, all results in the test or tables are presented as median and interquartile range (IQR), or as the numbers (percentages) of patients. Categorical variables were analyzed using Pearson's chi-square tests or Fisher's exact tests. Continuous variables were analyzed using Mann-Whitney *U* tests. Spearman's correlation coefficients, rho (ρ), were used to assess whether there was a relationship between PF ratio at the time of presentation and clinical outcomes, including resolution of associated symptoms and signs, and intensive care unit (ICU) stay. In order to compare the efficacies of two weeks vs. four weeks of corticosteroid treatment, differences in baseline characteristics

between the two groups were adjusted if the *p*-value was less than 0.2 [11]. Adjusted mean time to resolution of individual clinical symptoms was calculated using a general linear model. Adjusted proportion of patients with pulmonary infiltration on HRCT at day 14 was calculated by logistic regression analysis. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

During the study period, 160 patients suspected to have AEP were entered into the registry. Out of these patients, 22 (14%) patients were excluded because eosinophils on BAL were less than 25%, even though it was also increased (12 – 25%). In addition, a patient diagnosed with 2009 influenza A (H1N1) associated AEP [12] was excluded from the study. Ultimately, 137 patients with a definite diagnosis of AEP were included in this study.

Clinical Characteristics

The clinical characteristics at the time of presentation of 137 patients with AEP are shown in Table 2. All patients were young male with a median age of 20 (IQR, 19 – 21) years. One hundred thirty five (99%) patients were current smokers. In the month prior to developing AEP, 71 of these patients had started smoking with no previous history of smoking, 41 had restarted smoking after at least one year of cessation, and 13 had increased the number of cigarettes smoked per day. Of the 125 patients who had recently changed their smoking habits, the time from initiation of smoking or increased number of cigarettes to presentation of symptoms was 17 days (ranging from 13 to 26). Sixteen (12%) patients had a pre-existing allergic disease. However, other causes related pulmonary eosinophilia were not found. Most common symptoms were cough (95%), dyspnea (92%), and fever (88%). The level of fever was higher in patients with chills (38.2 [37.4 – 39.0] ˚C) compared to those of patients without chills (37.2 [37.2 – 38.2] ˚C) ($p < 0.001$). Inspiratory crackles were present on chest auscultation in 92 (67%) patients. A total of 108 (79%) patients were admitted to the ICU and 29 (21%) patients to a general ward. Eighty (58%) patients presented with respiratory failure with decreased oxygenation (PF ratio < 300); however, mechanical ventilation was needed for only three (2%) patients, two of whom were intubated.

Laboratory Findings

Laboratory findings at the time of presentation are shown in Table 1. Leukocytosis of peripheral blood (>10,000/μL) was seen in 97 (71%) patients. Eosinophilia (>500/μL) was detected in the peripheral blood of 44 (32%) patients whose median level of eosinophil was 719 (593 – 997) /μL. The median PF ratio at initial presentation was 284.3 (232.7 – 334.1). Bronchoscopy with BAL was performed in all patients on the day of presentation, and the median percentage of eosinophils on BAL fluid was 40% (35 – 53). The percentage of lymphocyte fluid was also elevated with a median of 19% (12 – 28). There were no bacterial, fungal, or parasitic isolates from BAL fluid.

Radiological Findings

HRCT findings at the time of presentation are shown in Table 3. The most common finding was ground glass opacity in 133 (97%) patients, followed by pleural effusion in 121 (88%) patients. Interlobular septal thickening was present in 93 (68%) patients. Centrilobular nodules were present in 71 (52%) patients and all cases had poorly defined centrilobular nodules. In addition, air-space consolidation was found in 51 (37%) patients and thickening of bronchovascular bundles was present in 24 (18%) patients. However, air-space consolidation were more frequently observed in patients with respiratory failure compared to patients without respiratory failure (47% vs. 19%, $p = 0.002$).

Treatment Response and Follow-up

A total of 127 (92%) patients were treated with corticosteroids at the time of AEP diagnosis (Table 4). Among them, 90 patients were administered intravenous methylprednisolone for three days followed by oral prednisolone and 37 patients received oral prednisolone only.

Forty-two patients received a four-week course of treatment and 85 patients received a two-week course of treatment. The remaining ten (7%) patients did not receive corticosteroid treatment at all, based on their symptoms and degree of oxygenation, but improved spontaneously. All symptoms improved after a median of seven (4 – 10) days; defervescence occurred within 48 hours in all patients and dyspnea was improved within a median of 3 (2 – 5) days. Median counts of peripheral eosinophil decreased to 129 (48 – 472) at 7 days after corticosteroid treatment. However, the eosinophil counts increased again at 14 days (284 [92 – 743]) after the treatment compared to those at 7 days after the treatment. This trend was also observed in frequencies of eosinophilia (>500/μL) after the treatment (24% at 7 days and 36% at 14 days) (Table 4). At seven days, both pulmonary infiltrates and pleural effusion were still visible on chest radiographs in 19 (15%) patients. HRCT taken at 14 days showed pulmonary infiltrates present in 13 (10%) patients and pleural effusion present in three (2%) patients. Adverse effects were noted in 25 (20%) patients. One patient developed herpes zoster, 12 (9%) patients developed epigastric pain, and 14 (11%) patients developed dyspepsia.

Severity of respiratory failure as measured by PF ratios correlated inversely with improvement of dyspnea ($\rho = -0.329$, $p < 0.001$), discontinuation of oxygen ($\rho = -0.463$, $p < 0.001$), and ICU stay ($\rho = -0.287$, $p = 0.003$) (Table 5).

All patients were discharged with complete resolution of symptoms and radiologic abnormalities. A total of 42 (31%) patients were followed up a median of 74 (60 – 153) days after discharge from the hospital. Of these 42 patients, 23 (55%) of them started smoking again, but an AEP relapse occurred in only one patient who resumed smoking 44 days after stopping cigarette smoking.

Comparison of Efficacy of Two Week vs. Four Week Corticosteroid Treatments

Comparisons of baseline characteristics of patients who received two weeks and four weeks of corticosteroid treatment are summarized in Table 6. Patients who received corticosteroid treatment for four weeks were more likely to have a fever and inspiratory crackle on chest auscultation when compared with those who received corticosteroid treatment for two weeks. CRP levels and neutrophil counts in BAL fluid were significantly higher and PF ratio was significantly lower in the four-week group. After adjusting for fever, myalgia, crackle on chest auscultation, CRP, peripheral eosinophilia, and neutrophil count in BAL fluid, the mean and proportion of patients were calculated in order to compare the efficacy of corticosteroid treatment between the two-week and four-week groups (Table 7). Differences in adjusted means (95% CI) for times to defervescence, resolution of dyspnea, and disappearance of all symptoms were 0.11 (-0.26 – 0.49) days, 0.57 (-0.71 – 1.86) days, and -0.04 (-1.91 – 1.83) days, respectively. The difference in adjusted proportion for patients whose pulmonary infiltration was visible on HRCT at 14 days was 6.92% (-8.19 – 22.02). In addition, the frequency of adverse effects was similar between the two-week group and four-week group (18% vs. 24%, $p = 0.411$).

Disscusion

AEP is thought to be a rare disease and there is a limited number of case series, all with relatively small sample sizes, that have been reported in the medical literature [1, 3, 5, 6, 10, 13-15]. That said, studies with larger samples afford the best picture of the clinical characteristics of this disease. Although the present study data came from a single center referral military hospital, 137 cases of AEP were identified. The main reason why very high number of patients could be collected in a single center over relatively short period is come from the unique characteristics of medical system in Korea army. According to the military law of Korea army, all soldiers should be treated in military hospitals. Armed Forces Capital Hospital is the only tertiary referral military hospital in Korea where bronchoscopy is available. Accordingly, all patients with suspected AEP should be transferred to the Armed Forces Capital Hospital. Although this study is single center experience, enrolled patients were transferred from more than 20 military hospitals. Therefore, our cohort represented entire young men at risk for AEP in Korean army. This relatively large case series confirms clinical characteristics, radiological findings and responsiveness to standardized corticosteroid treatment previously reported in smaller case series [2]. Additionally, this series indicates that a two week short course of corticosteroid treatment might be acceptable for treatment of AEP with respiratory failure.

The etiology of AEP is unknown, but several series have suggested that cigarette smoke is related to the onset of AEP [3, 5, 7]. Most of the patients (99%) in this study were current smokers, and the majority had either restarted smoking after cessation or had started smoking for the first time within one month prior to presentation. The median duration from initiation of smoking to presentation of symptoms was 17 days, which is consistent with previous reports [3, 9]. Additionally, within one month before onset of AEP, 13 patients

increased the number of daily cigarettes they smoked. Therefore, the study results support the theory that recent changes in smoking habits, including restarting after cessation and increasing the number of daily cigarettes, are associated with the development of AEP [3].

Hypoxemic respiratory failure is frequently identified at presentation and often requires mechanical ventilation in patients with AEP. In the present study, about 60% of the patients presented with acute respiratory failure with decreased oxygenation. However, mechanical ventilation was required in only three patients. In addition, some patients did not progress to severe respiratory failure and then had a spontaneous recovery without any treatment. Interestingly, 16% – 27% of patients were improved without definite treatment in the previous studies [5, 14]. Uchiyama et al.[3] reported that the majority of patients with AEP spontaneously improved without any treatment. Therefore, the clinical course and severity of AEP appear to be even more varied than originally reported [1].

Although spontaneous improvements have been reported even in patients with severe respiratory failure [5], death from AEP with respiratory failure can occur [7, 16]. In earlier case series, therefore, treatments with a high dose of corticosteroid were initiated and rapid improvements were reported [1, 6, 17-19]. In the present study, patients with AEP were uniformly responsive to intravenous or oral corticosteroid treatment. Interestingly, the improvements of clinical outcomes were correlated with severity of respiratory failure at presentation. In addition, the majority of pulmonary infiltrates on chest radiographs disappeared within seven days after corticosteroid treatment, which is consistent with previous reports [7]. However, when some patients were evaluated with CT scan at 14 days, pulmonary infiltrates and pleural effusion were still present. During the follow-up period, relapse occurred in only one patient who resumed smoking 1.5 months after cessation of cigarette smoking. Although previous reports had suggested that no relapses occurred in patients recovered from AEP, three additional cases of relapsed AEP are reported in the recent

literature [3, 20, 21]. Interestingly, cases involving AEP relapse, including the relapse reported in the present study, are associated with resumption of smoking after temporary cessation of smoking. These observations suggest that relapse of AEP can occur in patients who resume cigarette smoking. However, the remaining 23 patients who resumed cigarette smoking in this study did not have an AEP relapse.

There is no standardized regimen of corticosteroid treatment for AEP. The literature discusses proposed and implemented regimens of corticosteroid that span a wide range of doses and durations [2]. A commonly recommended regimen is methylprednisolone 60 – 125mg intravenously every six hours, changing to 40 – 60 mg of oral prednisone daily with a taper over two to six weeks [22]. However, the optimal duration of corticosteroid treatment is uncertain and has not been subjected to controlled trials [4]. This is the first study that showed clinical efficacy of standardized treatment of corticosteroid for AEP. Patients in this study were treated according to the standardized corticosteroid protocol based on the severity of disease [22], but we changed the duration of the taper from four weeks to two weeks. This made it possible to compare the efficacy and safety of two-week vs. four-week courses of treatment. Interestingly, the efficacy of a two-week course of corticosteroid was similar to that of a four-week course in terms of time to resolution of clinical symptoms and resolution of radiological abnormalities. In addition, the frequency of adverse effects was also similar between the groups. These might be because a similar dosage of corticosteroid is administered during the first week of treatment in both the two week and four week regimen (Table 1). The primary difference between the regimens was the corticosteroid tapering schedule. Therefore, the results of this study suggest that high doses of corticosteroid could be tapered over periods as short as ten days. This is supported by the results of previous studies [1, 6]. In addition, recently reported cases from Japan received only high doses of corticosteroids intravenously for three days without a maintenance treatment of oral

prednisolone [3]. However, these observations should be further evaluated by a prospective study.

There are several limitations to this study. First, given its retrospective nature, there is always the possibility that selection bias might have influenced the significance of our findings. However, the data were collected prospectively from all consecutive patients with AEP. Patient history, especially in terms of smoking, AEP confirmation tests, and corticosteroid treatment was taken according to standardized protocol. In addition, this study was conducted at a single military hospital and all of the enrolled patients were young males, which may limit the ability to generalize our findings to other centers or populations. However, previous reports showed that AEP develops predominantly in young patients [1, 3, 5, 7]. The third limitation of this study is that baseline characteristics of patients were not balanced when comparing the efficacies between short and long courses of corticosteroid treatment. This was addressed by the adjusted multivariate analysis. However, the potential for bias due to an unmeasured confounder remains.

In conclusion, in addition to further clarifying the major clinical characteristics of AEP and the association between recent changes in smoking habits and development of AEP, this study suggests that respiratory symptoms of AEP can vary from mild dyspnea to life-threatening respiratory failure. This study also found that two weeks of corticosteroid treatment for patients with respiratory failure could be as effective as four weeks of treatment, although this observation needs to be further evaluated by a prospective study.

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Table 1. Standardized treatment protocol for acute eosinophilic pneumonia at the Armed Forces Capital Hospital.

Days	Four week course of treatment		Two week course of treatment	
	Respiratory failure (+)	Respiratory failure (-)	Respiratory failure (+)	Respiratory failure (-)
D1	Intravenous methylprednisolone 60mg every 6 hr	Oral prednisolone 30 mg twice a day	Intravenous methylprednisolone 60mg every 6 hr	Oral prednisolone 30 mg twice a day
D2				
D3				
D4	Oral prednisolone 30 mg twice a day		Oral prednisolone 30 mg twice a day	
D5				
D6				
D7				
D8			Oral prednisolone 20 mg twice a day	Oral prednisolone 20 mg twice a day
D9				
D10				
D11	Oral prednisolone 25 mg twice a day	Oral prednisolone 25 mg twice a day	Oral prednisolone 20 mg once a day	Oral prednisolone 20 mg once a day
D12				
D13			Oral prednisolone 10 mg once a day	Oral prednisolone 10 mg once a day
D14	Oral prednisolone 20 mg twice a day	Oral prednisolone 20 mg twice a day		
D15				
D16				
D17	Oral prednisolone 15 mg twice a day	Oral prednisolone 15 mg twice a day		
D18				
D19				
D20	Oral prednisolone 15 mg once a day	Oral prednisolone 15 mg once a day		
D21				
D22				
D23	Oral prednisolone 10 mg once a day	Oral prednisolone 10 mg once a day		
D24				
D25				
D26	Oral prednisolone 5 mg once a day	Oral prednisolone 5 mg once a day		
D27				
D28				

Table 2. Clinical characteristics and laboratory findings at the time of presentation in 137 patients with acute eosinophilic pneumonia

Characteristics	No. (%) or median (IQR)
Age (years)	20 (19 – 21)
Sex (male)	137 (100)
History of allergic disease	16 (12)
Rhinitis	10
Dermatitis	3
Bronchial asthma	3
Smoking history	
Current smoker	135 (99)
Started smoking for the first time within one month of developing AEP	71
Resumed smoking within one month of developing AEP after past cessation	41
Increased number of cigarettes smoked per day within one month of developing AEP	13
No change in smoking habits	10
Former smoker	1 (1)
Never smoked	1 (1)
Time from initiation of smoking to presentation*, days	17 (13 – 26)
Symptoms	
Cough	130 (95)
Dyspnea	127 (93)
Fever	120 (88)
Chill	76 (56)
Headache	40 (29)
Myalgia	31 (23)
Chest pain	22 (16)
Inspiratory crackle on chest auscultation	92 (67)
Laboratory findings	
White blood cell count, /μL	12070 (9435 – 16835)

Leukocytosis (>10,000/μL)	97 (71)
Peripheral eosinophil count, /μL	360 (220 – 583)
Eosinophilia (>500/μL)	44 (32)
C-reactive protein, mg/dL	16.6 (9.1 – 36.6)
PF ratio	284.3 (232.7 – 334.1)
Eosinophils on BAL, %	40 (35 – 53)
Lymphocytes on BAL, %	19 (12 – 28)
Neutrophil on BAL, %	5 (2 – 11)
Admitted to ICU	108 (79)
Need for mechanical ventilation	3 (2)
Invasive	2
Non-invasive	1

IQR, interquartile range; PF ratio, arterial partial pressure of oxygen/fraction of inspired oxygen; BAL, bronchoalveolar lavage; ICU, intensive care unit

* Time from initiation of smoking or increased number of cigarettes to presentation of symptoms in 125 patients who had changed their smoking habits.

Table 3. High-resolution computed tomography (HRCT) findings at the time of presentation in 137 patients with acute eosinophilic pneumonia

HRCT findings	No. of patients (%)
Ground glass opacity	133 (97)
Interlobular septal thickening	93 (68)
Centrilobular nodules	71 (52)
Air-space consolidation	51 (37)
Thickening of bronchovascular bundles	24 (18)
Pleural effusion	121 (88)
Bilateral	107
Unilateral	14

Table 4. Treatment responses in 127 patients with acute eosinophilic pneumonia who received corticosteroid treatment

	No. (%) or median (IQR)
Corticosteroid treatment	127 (93)
IV methylprednisolone followed by oral prednisolone	90
Oral prednisolone only	37
No treatment	10 (7)
Clinical outcomes	
Time to defervescence, days	0 (0 – 1)
Time to improved dyspnea, days	3 (2 – 5)
Time to discontinuation of oxygen supplement, days	2 (0 – 4)
Time to disappearance of all symptoms, days	7 (4 – 10)
Duration of ICU stay, days	2 (2 – 3)
Mortality	0 (0)
Laboratory outcomes	
Peripheral eosinophil count at 7 days, /μL	129 (48 – 472)
Eosinophilia (>500/μL) at 7 days	31 (24)
Peripheral eosinophil count at 14 days, /μL	284 (92 – 743)
Eosinophilia (>500/μL) at 14 days	46 (36)
C-reactive protein at 7 days, mg/dL	0.28 (0.13 – 0.50)
C-reactive protein at 14 days, mg/dL	0.13 (0.02 – 0.50)
Radiological outcomes	
Pulmonary infiltrates visible on chest radiograph at 7 days	19 (15)
Pleural effusion visible on chest radiograph at 7 days	19 (15)
Pulmonary infiltrates visible on HRCT at 14 days	13 (10)
Pleural effusion visible on HRCT at 14 days	3 (2)
Adverse effect of corticosteroid	25 (20)
Herpes zoster	1 (1)
Epigastric pain	12 (9)
Dyspepsia	14 (11)

IV, intravenous; ICU, intensive care unit; HRCT, high-resolution computed tomography

Table 5. Correlations between PF ratios and clinical outcomes

Clinical outcomes	Correlation coefficient (ρ)	*P* value
Time to defervescence, days	-0.071	0.411
Time to improved dyspnea, days	-0.329	< 0.001
Time to discontinuation of oxygen supplement, days	-0.463	< 0.001
Time to disappearance of all symptoms, days	-0.146	0.090
Duration of ICU stay, days	-0.287	0.003

PF ratio, arterial partial pressure of oxygen/fraction of inspired oxygen; ICU, intensive care unit

Table 6. Comparisons of baseline characteristics of patients who received corticosteroid treatment for two weeks and four weeks

Characteristics	Two-week group (n = 85)	Four-week group(n = 42)	*P* value
Age (years)	20 (20 – 21)	20 (20 – 21)	0.863
History of allergic disease	8 (10 %)	3 (10 %)	1.000
Time from initiation of smoking to presentation*, days	17 (14 – 28)	16 (11 – 24)	0.435
Symptoms			
Cough	80 (94%)	40 (95%)	1.000
Dyspnea	78 (92%)	41 (98%)	0.269
Fever	69 (81%)	41 (98%)	0.011
Chill	46 (54%)	26 (62%)	0.405
Headache	28 (33%)	11 (26%)	0.438
Myalgia	27 (32%)	3 (7%)	0.002
Chest pain	13 (15%)	5 (12%)	0.606
Inspiratory crackle on chest auscultation	53 (62%)	35 (83%)	0.016
Laboratory findings			
Leukocytosis (>10,000/μL)	59 (69%)	33 (79%)	0.277
Peripheral eosinophilia (>500/μL)	32 (38%)	8 (19%)	0.034
C-reactive protein, mg/dL	12.1 (5.9 – 31.4)	35.6 (16.3 – 38.4)	< 0.001
PF ratio	298.7 (262.9 – 344.8)	239.1 (219.3 – 268.8)	< 0.001
Eosinophils on BAL, %	40 (35 – 53)	40 (31 – 50)	0.078
Lymphocytes on BAL, %	19 (12 – 26)	23 (12 – 30)	0.747

Neutrophil on BAL, %	5 (2 – 10)	6 (4 – 17)	0.004

PF ratio, arterial partial pressure of oxygen/fraction of inspired oxygen; BAL, bronchoalveolar lavage

* Time from initiation of smoking to presentation was available in 131 patients (97%) who were current smokers.

Data are presented as median (interquartile range) or number (%).

Table 7. Comparison of adjusted means or proportion of clinical outcomes of patients who received corticosteroid treatment for two weeks and four weeks

Clinical outcomes		Adjusted mean or proportion (95% CI)*	Difference between adjusted means or proportions (95% CI)
Time to defervescence, days	2 weeks	0.66 (0.48, 0.84)	0.11 (-0.26, 0.49)
	4 weeks	0.54 (0.24, 0.85)	
Time to improved dyspnea, days	2 weeks	3.84 (3.23, 4.45)	0.57 (-0.71, 1.86)
	4 weeks	3.27 (2.22, 4.31)	
Time to disappearance of all symptoms, days	2 weeks	7.21 (6.32, 8.09)	-0.04 (-1.91, 1.83)
	4 weeks	7.25 (5.73, 8.76)	
Pulmonary infiltration (+) at D14, %	2 weeks	12.98 (5.83, 20.12)	6.92 (-8.19, 22.02)
	4 weeks	6.06 (-6.17, 18.28)	

*Adjusted mean was calculated by general linear model and adjust proportion by logistic regression analysis, after adjusting for differences in fever, myalgia, crackle on chest auscultation, C-reactive protein, peripheral eosinophilia, and neutrophil count on BAL fluid.