INHALED CORTICOSTEROIDS IN THE TREATMENT OF CHRONIC EOSINOPHILIC PNEUMONIA

KRONİK EOZİNOFİLİK PNÖMONİ TEDAVİSİNDE İNHALE KORTİKOSTEROİDLER

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ABSTRACT: Chronic eosinophilic pneumonia (CEP) is a rare disease which responds favourably to corticosteroid (CS) treatment. However, there is no consensus regarding the initial CS dose and duration of treatment. The major complication is the relapse of the disease upon tapering or discontinuation of CS treatment. The role of inhaled corticosteroids in CEP patients has not been evaluated, although a decreased frequency of relapse has been previously reported in CEP patients with asthma receiving inhaled corticosteroids.

We decided to administer oral plus inhaled CS therapy in seven patients with CEP in whom relapse occurred during long-term follow-up.

Inhaled CS treatment resulted in a reduced need for oral CS without causing an increase in relapse rate or obstructive lung function defect.

By using inhaled and oral CS combination, the lowest dose of oral CS should be determined individually, and a long-term follow up should be planned in relapses.

Key words: Chronic eosinophilic pneumonia, treatment, inhaled corticosteroids

ÖZET: Kronik eozinofilik pnömoni (KEP) kortikosteroidlere iyi cevap veren nadir görülen bir hastalıktır. Bununla birlikte kortikosteroid (KS) başlangıç dozları ve tedavi süresini belirleyen ortak görüş yoktur. En önemli komplikasyon ks dozu azaltılırken veya kesildiğinde gelişen nükslerdir. KEP ile birlikte astımı olduğu için inhale KS alan hastalarda nüks sıklığının daha az olduğu bildirilmekle birlikte KEP hastalarında inhale KS'lerin rolü belli değildir.

Uzun süreli takipte relaps gelişen 7 KEP hastasına oral KS ile beraber inhale KS verilmesi planlandı.

İnhale KS tedavisi nüksleri ve obstrüktif solunum fonksiyon bozukluğunu artırmadan oral KS ihtiyacını azaltmıştır.

İnhale ve oral KS'ler birlikte kullanılarak en düşük oral KS dozu kullanılabilir ve nükslerde uzun dönem izlem planlanmalıdır.

Anahtar Kelimeler: Kronik eozinofilik pnömoni, tedavi, inhale kortikosteroidler

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INTRODUCTION

Chronic eosinophilic pneumonia (CEP) is a rare disease of unknown etiology.[1] The diagnosis is usually based on the following: i) presence of respiratory and systemic symptoms lasting more than 2 weeks; ii) alveolar and/or blood eosinophilia; iii) characteristic peripheral pulmonary infiltrations in the chest X-ray; and iv) exclusion of other causes that are associated with eosinophilic lung disease.[2] A dramatic response to oral corticosteroids along with clinical and radiological findings allows the diagnosis of chronic eosinophilic pneumonia (CEP) without histopathological examination.[1,3] The actual prevalence of CEP is not known [2]. Although all age groups can be affected, CEP is rare in pediatric patients[3-6]. Female to male ratio of the disease is 2:1.[3, 4, 7] One third to one half of the patients have a history of asthma[1, 7-10], with less than 10% of the cases being current smokers.[3, 4, 7] The major complication during the course of CEP is the occurrence of relapses which usually develop following the discontinuation or dose reduction of CS. Most patients require long term steroid treatment.[7, 8, 11]

METHODS

Between 1997 and 2007, a diagnosis of CEP was made in seven patients (four males, three females) attending to our clinic with respiratory and systemic symptoms lasting more than 2 weeks in addition to characteristic peripheral pulmonary infiltrations, and alveolar and/or blood eosinophilia. The diagnosis was further confirmed by observation of a dramatic response to oral CS.

RESULTS

None of the patients had a history of medication use or parasitic infection that may result in blood eosinophilia. Also, there were no clinical signs suggestive of vasculitis, and no patients were tested positive for antinuclear cytoplasmic antibody (ANCA). Radiological examination showed no bronchiectasis, skin and serologic tests for aspergillus fumigatus were negative. Clinical characteristics of the patients are shown in Table 1. The mean age at presentation was 33.7 years (range 19-52), with no current smokers, and only one patient had a past history of smoking (patient no. 4). Four patients had a prior history of asthma, and the remaining three patients did not develop asthma during the follow-up. The presenting complaints were as follows: dry cough, weight loss and dyspnea (five patients), wheezing (four patients), chest pain and productive cough (one patient). Clinical signs at the time of diagnosis included wheezing, crepitations and rhonchi.

Histopathological examination of lung parenchyma was done in three patients. Samples were obtained by open lung biopsy in two patients and by transbronchial biopsy in one. Microscopically, eosinophilic infiltration was detected in the interstitium and alveolar lumen of these three patients.

Biological Features

Data are summarized in Table 1. All patients had a raised absolute eosinophil count at the time of diagnosis (mean: 2527/mm^3; range: 1300-4200/mm^3). Erythrocyte sedimentation rate (ESR) was elevated in four patients. Serum Ig E levels were elevated in four out of seven patients (range: 16- 1100 KIU/L). Three of these patients had asthma prior to the onset of CEP. Bronchoalveolar lavage (BAL) was done in two cases.

Radiological Features

A postero-anterior chest radiograph was obtained in all patients at the time of diagnosis. Five patients had characteristic peripheral opacities, while atypical opacities were observed in one patient. Chest radiograph was normal in the remaining one patient. Chest computed tomography (CT) scan was performed in all patients, which showed ground glass opacities in 3 patients, consolidation in 2 patients, and a combination of the two in the remaining two patients (Figure 1). In five patients, the lesions were located peripherally, while they were widespread and extensive in the other two patients. Lesions were bilaterally located in all cases. Mediastinal lymph nodes and concentric subpleural lines were present in one patient.

Lung Function Tests

Five of our patients with CEP had abnormal lung function test results, with a restrictive pattern in one patient, and obstructive pattern in four patients with a history of asthma and atopy. Corticosteroid treatment alleviated these ventilatory abnormalities.

Table 1. Epidemiological, clinical and biological characteristics of patients.

Patiient No.	Age	Sex	Initial symptom	Previous asthma	Eosinophil count (mm3)	ESR (mm/h)	Method of diagnosis	Serum IgE (KUI/L)
1	49	F	DC, WL, P	No	2800	80	Open lung biopsy	1100
2	34	F	DC, D, WL	Yes (5 years)	1480	90	Open lung biopsy	222
3	52	M	W,D, PC,WL	Yes (2years)	3300	60	Transbronchial biopsy, Clinical, radiological	234
4	32	M	W,WL, DC, D	Yes (6 months)	1300	50	Clinical, radiological, BAL eosinophilia	32
5	19	F	DC	No	2110	26	Clinical, radiological, BAL eosinophilia	16
6	23	M	WL, DC, D,W	No	2500	10	Clinical, radiological	48
7	27	M	D,W	Yes (2 years)	4200	4	Clinical, radiological	385

M: male; F: female; DC: dry cough; WL: weight loss; P: chest pain; D: dyspnea; W: wheezing; PC: productive cough.

Treatment and Follow-up

The first detailed description of CEP was presented by Carrington et al, and since that time, oral corticosteroids have been the mainstay of treatment in CEP. All of our patients showed a rapid improvement in symptoms, blood eosinophilia, and radiographic infiltrates with oral corticosteroid therapy (OCST).

Follow-up data are summarized in Table 2. At follow-up, all patients were well, with six receiving combined oral and inhaled steroids as the maintenance treatment (5 patients 5 mg prednisolone every other day and 1000 mg/day inhaled fluticasone, and one patient 10 mg/day prednisolone and 1000 mg/day inhaled fluticasone) and one receiving 1000 mg/day inhaled fluticasone only. The latter received OCST for 15 months and had no relapse during follow-up, where the patient was maintained with inhaled steroids only. However a relapse occurred in the other six. In two cases, relapse was observed after OCST had been discontinued, and in four relapse occurred during the dose reduction phase. A relapse was de-

Table 2: Follow-up data

Patient no	"Initial dose* (mg)"	"Initial Evoluton"	"Dose at Relaps (mg)"	"Relapse Number"	"Time between treatment and relapse (months)"	"Duration of initial treatment (months) "	Maintenance steroid		Duration of follow-up (months)
							Oral (Mg)	Inhaler fluticasone (Mg)	
1	65	DI	-	1	33	36	5↑	1000	146
2	50	DI	5 5	2	-	12 22	5↑	1000	86
3	50	DI	-	-	-	15	-	1000	62
4	40	DI	10 10	2	-	4 6	10‡	1000	18
5	40	DI	5	1	-	8	5↑	1000	22
6	40	DI	-	1	2	14	5↑	1000	24
7	40	DI	10 10 5	3	-	4 15 6	5↑	1000	50

Pt: Patient DI.drammatic improvement

* initial prednisolone dose ↑: every other day ‡: day

fined as the recurrence of clinical and radiological signs. In patients with a relapse, the original initial OCST doses were commenced. Three patients had only one relapse, while two had two relapses, and one had three relapses. In the first case, relapse occurred 33 months after a prolonged course of (36 months) OCST. The treatment was re-initiated with inhaled steroid and OCST. In patient no 6, two months after the completion of the initial treatment of 14 months, a relapse developed. This patient was also given a combination of oral and inhaled steroids. In other four cases (no 2, 4, 5, and 7) relapse occurred upon the reduction in oral steroid dose, and following the second relapse, oral and inhaled steroids were given concurrently. Apart from the case no. 7 with compliance problems, no further relapses were observed during the maintenance treatment of these patients with oral plus inhaler steroids. And a third course of combined treatment was commenced in case no. 7 with controlled disease activity for approximately two years.

DISCUSSION

Chronic eosinophilic pneumonia (CEP) was first described by Carrington et al. in 1969 in a series involving 9 patients.[1] Although a favourable early course has been reported for CEP[1, 4, 10, 12], long-term outcome remains relatively unclear. Pearson and Rosenow[10], Jederlinic et al.[4], Naughton et al.[7], Durieu et al.[11], and Marchand et al.[3] followed 8, 19, 12, 19, and 46 patients for an average duration of 6, 4, 10.2, 4, and 6.2 years, respectively. However, until now no definite consensus has been reached over the initial dose and duration of OCST, the role of continued treatment, the value of adding inhaled steroids to OCST, and the comparative efficacy of the combination in maintenance and in preventing relapses.[3, 4, 7, 10, 11] On the other hand, these studies clearly demonstrate a positive association between the relapse incidence and the duration of follow up with relapse rates of 47%, 69%, and 83% in the studies by Durieu, Marchand, and Naughton, respectively. Notably, these authors do hold the view that CEP not only affects the alveoli and interstitium , but also the airways. In CEP patients with a history of atopy and/or asthma using inhaled steroids, a lower relapse rate has been observed.[8] In our study, based on these observations we evaluated the role of inhaled steroids in the long-term follow-up and treatment of seven patients with CEP.

All of our patients met the diagnostic criteria of CEP as defined by Carrington et al.[1] with respiratory and systemic symptoms (wheeze, dyspnea, weight loss) lasting more than 2 weeks. Additionally, classical hematologic and radiographic findings were observed. For instance, peripheral blood eosinophilia was present in all patients while the ESR was markedly elevated in four. Furthermore, chest radiographs at the time of diagnosis showed the characteristic fluffy opacities at the lung periphery.[13] Three of our patients showed ground glass opacities without clear consolidation on CT. This pattern probably reflects relatively discrete eosinophilic alveolitis.[3] Bilateral infiltrates were present on CT in all patients. A striking feature is the absence of bronchiectasis in CEP, in contrast to allergic bronchopulmonary aspergillosis, another disease with migratory pulmonary infiltrates associated with blood and alveolar eosinophilia.[14] Interestingly, a history of asthma was present in four of 7 patients. While there is an association between preexisting asthma and CEP, an atopic history or existing asthma is not a prerequisite for the development of CEP[15]. In addition, serum IgE level was elevated in four patients, three of whom had a history of asthma.

A dramatic response to OCST was observed in all of our CEP patients, with prompt improvement in clinical and radiological findings. Following the re-admission of our first case with relapse that occurred 33 months after the completion of the initial 3 years of treatment, we re-assessed the long-term treatment protocol in our clinic and decided to attempt discontinuation of OCST in the remaining patients. When relapse occurred in patient no.1 and no.6, we commenced treatment with 1000 mg of fluticasone in addition to original OCST doses that were administered at the time of the diagnosis. These two patients still receive 1000 mg of fluticasone daily and 5 mg of OCST every other day. Therefore, our initial policy was to administer the original OCST dose if a relapse occurred during gradual tapering and to re-attempt discontinuation thereafter. However, in these patients relapse occurred again and original OCST dose was combined with inhaled steroid treatment. In one patient with asthma (patient no.3), who is on inhaled steroids, no relapse occurred during 4 years of follow

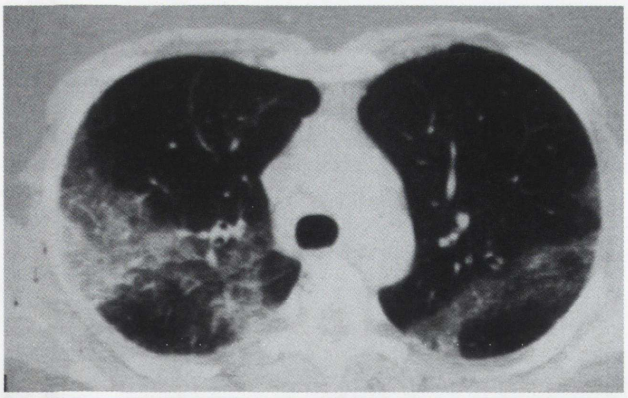

Figure 1: Consolidation and ground glass opacities in periphery of upper lobes, bilaterally.

up. In other 6 patients inhaled steroid dose was not altered during the maintenance, but lower doses of OCST were sufficient to prevent the relapses during follow-up.

In patients with CEP, there is no consensus over the optimal treatment of relapses, and some questions still remain unanswered regarding the initial dose of OCST, dose to be administered at re-initiation of OCST, role of high dose of inhaled steroids in combination with stable doses of OCST, or use of short-term oral steroid (1 mg/kg/day) combined with high dose inhaled steroids.

Current data indicate a high relapse rate (over 80%) in patients discontinuing OCST[7], suggesting the need for long-term treatment.[7, 8, 11, 15] But, the long term steroid use is definitely associated with its own risks, and no prospective studies have assessed this issue in patients with CEP, except for a case report by Lavandier and Carre concerning long-term treatment with inhaled steroids in a single patient.[16] Interestingly, an attempt to reduce the dose of OCST was made on five different occasions, all ending up with relapses, and after detecting new opacities in the chest x-ray after the sixth attempt, this patient was put on high dose inhaled steroids combined with OCST, which resulted in disease control. During a one-week period, OCST was discontinued, and the patient had no further relapses with high-dose inhaled steroid alone. On the other hand, when the investigators attempted to reduce the dose of inhaled steroid, exacerbations occurred in three different occasions which were treated again with high dose inhaled steroids and short-term use of 40 mg/day OCST. In a review by Alam and Burki, CEP patients receiving inhaled steroids alone for maintenance treatment up to 8 years have been described.[15] In the study by Naughton, in only two of the 12 patients no relapse occurred in the long-term after steroid was discontinued. Additional inhaled steroids were given to five patients, three of whom required reduced maintenance doses.[7] In another study, long-term treatment with inhaled steroids in CEP patients with asthma resulted in a lower relapse rate (56% vs. 23%) and reduced number of annual relapses (median 0.24 vs. 0). These findings suggest the presence of a strong interaction between CEP and asthma with a reduced relapse rate in patients receiving inhaled steroids. Another interesting observation in that study was the association between CEP and severe and worsening asthma, and the need for long-term OCST treatment in more than one third of the patients.[8]

In conclusion, inhaled steroids appear to suppress the disease activity, allow reduced maintenance steroid doses without increasing the relapse rate, and help to prevent airway obstruction in patients with CEP. However in these patients relapses can occur years after the initial treatment. In patients receiving combined oral and inhaled steroids, long-term follow up, as in our patients, is warranted to fully appreciate the role of this treatment modality in CEP.

The questions that remain unresolved in the treatment of CEP are as follows:

- Should we administer a combination of oral and inhaler steroids at the initiation of treatment?
- Should we continue inhaled steroids after OCST is discontinued?
- How should the relapses be treated?
- Do inhaled steroids suffice for maintenance treatment? Or should they be combined with OCST?

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