Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2022; 61 (4): 524-529

Systemic corticosteroid treatment response in hypersensitivity pneumonitis: a single center experience

Hipersensitivite pnömonisi hastalarında sistemik kortikosteroid tedavi yanıtı: bir tek merkez deneyimi

Nilüfer Aylin Acet Öztürk, Funda Coşkun, Ahmet Yurttaş, Nurlana İbrahimova, Özge Aydın Güçlü, Ezgi Demirdöğen, Aslı Görek Dilektaşli, Ahmet Ursavaş, Esra Uzaslan, Mehmet Karadağ

Uludağ University Faculty of Medicine, Department of Pulmonology, Bursa, Türkiye

ABSTRACT

Aim: Hypersensitivity pneumonitis (HP) is defined as an inflammatory and/or fibrotic immune reaction provoked by an inhalational exposure in susceptible individuals. Initial management of HP patients includes remediation of exposure and treatment with immunosuppressive agents. In this study we aimed to define clinical features and treatment modalities and to evaluate response to corticosteroids in HP patients followed in a single tertiary care setting.

Materials and Methods: The patients with HP diagnosis followed between 1 January 2019 and 31 December 2020 were included in this retrospective study. Firstly, the candidate factors related with treatment response were evaluated by univariate analysis and then the possible factors with p values below 0.15 were evaluated by multiple linear regression model to identify independent predictors of systemic corticosteroid response.

Results: The study population consisted of 50 HP patients and 20 of them (40%) had fibrotic HP. Forty-one (82.0%) patients were followed with a medical treatment for longer than 3 months. Within follow-up period 15 (36.5%) patients didn't show clinical or radiological response to systemic corticosteroids. Patients without treatment response were presented as fibrotic HP (66.6% vs 26%, p=0.02), had radiological features of fibrosis (86.6% vs 30.7%, p=0.002) and had loss of pulmonary functions (60.0% vs 34.6%, p=0.03) more frequently. Uni-variable analysis revealed that radiological features of fibrosis (OR: 0.07 [95%CI: 0.01-0.42], p=0.003) and mosaic attenuation (OR: 7.0 [95%CI: 0.30-10.07], p=0.08) in HRCT related with corticosteroid treatment response.

Conclusion: Our study suggests radiological features of fibrosis relate with worse clinical and radiological response to corticosteroid treatment. Prospective clinical trials are needed to clarify the role of immunosuppressive therapy in HP patients.

Keywords: Hypersensitivity pneumonitis, immunosuppressive treatment, corticosteroid, treatment response.

ÖZ

Amaç: *Hipersensitivite pnömonisi (HP) duyarlı bireylerde, inhalasyon yolu ile gelen maruziyetlere karşı gelişen inflamatuar ve/veya fibrotik bir immün yanıt olarak tanımlanmaktadır. HP hastalarının yönetimi maruziyetten kaçınmak ve immunsupresif ajanlarla tedaviyi içermektedir. Çalışmamızda bir üniversite hastanesinde takip edilen HP hastalarının klinik özelliklerini ve kortikosteroid tedaviye yanıtlarını değerlendirmeyi amaçladık.*

Corresponding author: Nilüfer Aylin Acet Öztürk
Uludağ University Faculty of Medicine, Department of Pulmonology, Bursa, Türkiye
E-mail: *niluferacet@gmail.com*
Application date: 03.02.2022 Accepted: 05.05.2022

Gereç ve Yöntem: *HP tanısı ile 1 Ocak 2019 ve 31 Aralık 2020 tarihleri arasında takip edilen hastalar retrospektif olarak çalışmaya dahil edildi. Tedavi yanıtı ile olasılıkla ilişkili faktörler öncelikte tek değişkenli olarak değerlendirildi. Sonrasında p değeri 0,15 ve altında olan faktörler çok değişkenli lineer regresyon modeli ile değerlendirilerek sistemik kortikosteroid yanıtı ile bağımsız ilişkili olan faktörler tanımlandı.*

Bulgular: *Çalışmamıza dahil edilen 50 HP hastasının 20 (%40,0)'ı fibrotik HP idi. Kırk bir (%82,0) hasta en az 3 aydır medikal tedavi almaktaydı. Takip süresince 15 (%36,5) hasta sistemik kortikosteroid tedavisine klinik veya radyolojik yanıt göstermedi. Tedavi yanıtı izlenmeyen olgular, sıklıkla fibrotik HP ile prezente olmakta (66,6% vs 26,0%, p=0,02), radyolojik olarak fibrozis bulguları göstermekte (%86,6 karşı %30,7, p=0,002) ve takiplerinde solunum fonksiyonlarında kaybı (%60,0 karşı %34,6, p=0,03) daha sık yaşamaktaydı. Tek değişkenli analizlerde radyolojik bulgulardan fibrozis varlığı (OR: 0,07 [95%CI: 0,01-0,42], p=0,003) ve mozaik atenüasyon bulgusu (OR: 7,0 [95%CI: 0,30-10,07], p=0,08) kortikositeroid tedavi yanıtı ile ilişkili bulundu.*

Sonuç: *Çalışmamız radyolojik olarak fibrozis bulgusunun varlığının kortikosteroid tedaviye kötü klinik ve radyolojik yanıt ile ilişkili olduğunu önermektedir. HP hastalarında immunsupresif tedavinin rolünün belirlenmesi için prospektif klinik çalışmalara ihtiyaç duyulmaktadır.*

Anahtar Sözcükler: *Hipersensitivite pnömonisi, immunsupresif tedavi, kortikosteroid, tedavi yanıtı.*

INTRODUCTION

Hypersensitivity pneumonitis (HP) is defined as an inflammatory and/or fibrotic immune reaction provoked by an inhalational exposure in susceptible individuals (1). Immunological mechanisms resulting in exaggerated humoral and cellular immune responses, inflammation, granuloma formation, and fibrosis are not clearly described (2, 3). In addition to different immune-pathogenesis, patients have different clinical and radiological presentations. Diagnosis of HP is based on exposure history, specific IgG response compatible with exposure, typical high resolution computed tomography (HRCT) features, bronchoalveolar lavage and pathological findings (3). Historically, patients were classified as acute, subacute, and chronic HP by disease duration and radiological features. The new ATS/JRS/ALAT Clinical Practice Guideline proposed classification according to the presence of fibrosis in HRCT because of the relationship between radiological features with histopathological stage and the importance of fibrosis in disease prognosis. Raghu et al. defined typical and compatible radiological findings in HP patients and classified HP patients as fibrotic HP or nonfibrotic HP (1).

Initial management of HP patients includes exposure remediation and treatment with immunosuppressive agents. Immunosuppressive treatment options include systemic corticosteroids, mycophenolate mofetil, azathioprine, and rituximab (2). In addition to these treatment options, antifibrotic treatment with nintedanib is an option for progressive fibrosing interstitial lung disease patients (4). However, optimal treatment management is not well documented in terms of medication choice, dosage, and treatment duration (3). Salisbury et al. suggested considering evidence of active inflammation for treatment decisions (5). Corticosteroid regimens with or without cytotoxic agents are considered as first line therapy (2, 5).

In this retrospective study, we aimed to define clinical features and treatment modalities, and to evaluate the response to corticosteroids in HP patients followed in a single tertiary care setting.

MATERIALS and METHODS

Patient selection, diagnosis, and treatment

Patients with an HP diagnosis followed between January 1, 2019 and December 31, 2020 were included in this retrospective study. The institutional ethical committee approved the study (protocol number: 2021-16/24). The medical records of patients were evaluated by two trained pulmonologists and a structured form was filled out. Exclusion criteria;1) Indefinite diagnosis of HP, 2) The follow-up duration was shorter than 3 months.

HP diagnosis was based on radiological evaluation as stated in the ATS/JRS/ALAT Clinical Practice Guideline (1), bronchoalveolar lavage cellular analysis, and surgical lung

biopsies. Detailed history for exposures capable of causing HP were evaluated. In indeterminate cases, diagnosis was reached through a multidisciplinary committee consisting of pulmonologists, chest radiologists and rheumatologists. Radiological features of fibrosis were the presence of honeycomb, traction bronchiectasis, reticulation and a three density 'head cheese' sign.

A treatment decision was made by the attending pulmonologist according to symptoms and pulmonary function tests. Medications were initiated after a period of exposure remediation, if the exposure could be identified. Patients received an initial dose of 0.75 – 0.5 mg/kg of corticosteroids with a physician dependent tapering schedule. Treatment response was evaluated every 3 months with symptom severity, pulmonary function tests and radiological images. If the patient didn't have any decrease in pulmonary symptoms, progression in radiological images and/or showed worsening in pulmonary function tests, then the patient was accepted as non-responsive to treatment.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 22.0 software program (IBM Corp., Armonk, NY, USA). Variables were investigated using histograms and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine distribution. Continuous data is described as the mean ± standard deviation or median (interquartile range) related to normally distributed or non-normally distributed, respectively. Categorical characteristics are described as numbers (%). Continuous outcome variables were compared between groups by a two-sample t-test for normally distributed data, and by a Mann–Whitney U-test for non-normally distributed data. The candidate factors related to treatment response were evaluated by univariate analysis and then possible factors with p values below 0.15 were evaluated by multiple linear regression model to identify independent predictors of systemic corticosteroid response. An overall %5 type-1 error level was used to infer statistical significance.

RESULTS

The study population consisted of 50 patients with mean age of 56.4 ± 13.0 years. Diagnosis was made with surgical lung biopsies in 18 (36.0%) patients. Seventeen (34.0%) patients didn't have any exposure. The known exposures were birds (38.0%), inorganic dust (14.0%), straw (12.0%) and organic dust (10.0%). The median duration of exposure was 12.0 [6.0 – 42.0] months. Ever-smokers were 36% of the population and had median 15.0 [7.0 – 31.2] package/year usage. The cardiovascular diseases were frequent among comorbidities. Ten (20%) patient had hypertension 8 (16%) patients had diabetes and 4 (8%) had coronary artery disease. The baseline characteristics of the study population are presented in Table-1.

The median follow-up of the study population was 8.0 [4.7-12.0] months. Forty-one (82.0%) patients were followed with a medical treatment for longer than 3 months. During this follow-up period, 15 (36.5%) patients didn't show clinical or radiological response to systemic corticosteroids. Eight (53.3%) patients in this non-response group didn't show any improvement with other medications such as azathioprine and mycophenolate mofetil. However, 3 (20.0%) patients presented clinical response to other treatments. Treatment related adverse events were present in 4 (18.2%) patients treated with corticosteroids. Comparison of groups according to response to systemic corticosteroids showed similar age, gender, comorbidities, and exposure history and baseline pulmonary functions. Patients without treatment response to systemic corticosteroids were presented as fibrotic HP, had radiological fibrosis findings, and had loss of pulmonary functions more frequently (Table-2). Univariable analysis revealed that radiological features of fibrosis and mosaic attenuation in HRCT were found as related to corticosteroid treatment response (Table-3).

Table-1. Baseline characteristics of study population (n=50).

Age (years)	56,4 ± 13,1
Male gender, *n(%)*	22 (44,0)
Smoker, *n(%)*	18 (36,0)
Symptoms, *n(%)*	
Dyspnea	47 (94,0)
Cough	40 (80,0)
Sputum	9 (18,0)
Classification according to new practice guideline, *n(%)*	
Fibrotic HP	20 (40)
Non-fibrotic HP	30 (60)
Radiological features, *n(%)*	
Fibrosis	25 (54,3)
Ground glass opacity	38 (82,6)
Mosaic attenuation	10 (21,7)
Bronchiectasis	15 (32,6)
Pulmonary functions	
FEV_1/FVC	80,7 ± 8,1
FEV_1 (%pred)	82,5 ± 21,3
FVC (%pred)	84,3 ± 21,1
DLCO (%pred)	55,0 ±21,3
DLCO VA (%pred)	77,2 ± 22,9
Prognosis, *n(%)*	
Hospitalization due to exacerbation	9 (18,0)
Loss of pulmonary functions	18 (36,0)
Radiological progression	5 (10,0)
All-cause mortality	3 (6,0)

Data was expressed as numbers (percentages), mean ± SD or median [IQR]. Definition of abbreviations: HP: hypersensitivity pneumonitis, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide

Tablo-2. Comparison of groups according to response to systemic corticosteroids, (n=41).

	Patients with no clinical response to systemic corticosteroids (n=15)	**Patients with clinical response to systemic corticosteroids (n=26)**	**p value**
Age, years	59,3 ± 14,6	54,1 ± 12,9	0,24
Male gender, *n(%)*	4 (26,6)	12 (46,1)	0,32
Smoker, *n(%)*	5 (33,3)	9 (34,6)	0,95
Bird exposure, *n(%)*	5 (33,3)	11 (42,3)	0,74
Symptoms, *n(%)*			
Dyspnea	14 (93,3)	24 (92,3)	1
Cough	11 (73,3)	22 (84,6)	0,43
Sputum	2 (13,3)	5 (19,2)	1
Classification, *n (%)*			
Fibrotic HP	10 (66,6)	7 (26,9)	0,02
Radiological features ,*n(%)*			
Fibrosis	13 (86,6)	8 (30,7)	0,002
Ground glass opacity	12 (80,0)	21 (80,7)	0,65
Mosaic attenuation	1 (6,6)	8 (30,7)	0,11
Bronchiectasis	6 (40,0)	6 (23,0)	0,47
Pulmonary function tests			
FEV_1/FVC	83,0 ± 5,8	78,0 ± 8,0	0,13
FEV_1 (%pred)	92,7 ± 21,5	80,7 ± 22,9	0,27
FVC (%pred)	91,7 ± 23,5	84,6 ± 22,0	0,48
DLCO (%pred)	56,0 ± 20,8	51,5 ± 20,0	0,61
DLCO VA (%pred)	73,8 ± 17,0	76,0 ± 241	0,77
Prognosis			
Follow-up duration, (months)	12.0 [11.0 – 43.7]	6.0 [4.0 – 10.0]	0,01
Hospitalization due to exacerbation, *n(%)*	3 (20,0)	6 (23,0)	1
Loss of pulmonary functions, *n(%)*	9 (60,0)	9 (34,6)	0,03
FEV_1 change (%)	-2.7 [-17.9 – 17.6]	4.4 [1.5 – 49.5]	0,31
FVC change (%)	-2,7 [-7.3 – 8.9]	8.1 [1.3 – 51.9]	0,15
DLCO change (%)	4.4 [-5.8 – 20.3]	24.2 [-7.6 -.83.2]	0,41
Radiological progression, n(%)	4 (26,6)	1 (3,8)	0,25
All-cause mortality, n(%)	1 (6.6)	1 (3.8)	1

Data was expressed as numbers (percentages), mean ± SD or median [IQR]. Definition of abbreviations: HP: hypersensitivity pneumonitis, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide

Table-3. Factors associated with corticosteroid treatment response.

	Univariable analysis			Multivariable analysis		
	OR	95%CI	p value	OR	95%CI	p value
Age	0.97	0.92-1.02	0.23	-	-	-
Gender	0.42	0.10-1.68	0.22	-	-	-
Baseline FEV_1/FVC	0.90	0.78-1.03	0.14	0.90	0.77-1.06	0.21
Fibrosis in HRCT	0.07	0.01-0.42	0.003	0.20	0.02-1.57	0.12
Mosaic attenuation in HRCT	7.0	0.30-10.07	0.08	1.61	0.10-24.9	0.73

Definition of abbreviations: FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, HRCT: high resolution computed tomography

DISCUSSION

In our study, patients with mosaic attenuation and without fibrosis in radiological evaluation had a better clinical and radiological response to corticosteroid treatment. These results are in accordance with some of the research in the literature. In their propensity score-matched cohort analysis, Ejima et al. have demonstrated improved survival, improved pulmonary functions, and slowed fibrotic progression with corticosteroids in patients without extensive fibrosis (6). De Sadeleer et al. have evaluated fibrotic HP patients and have showed survival are closely related to honeycombing in HRCT. In addition, the better corticosteroid response is seen in patients with higher bronchoalveolar lavage lymphocyte percentage and patients without honeycombing in HRCT (7). A new study evaluating the efficacy of 0.5 mg/kg/day methylprednisolone for 8 weeks in HP patients has shown improvement in FEV1, FVC, six-minute walking test parameters and oxygenation in both fibrotic and non-fibrotic patients. However, corticosteroid treatment has better effects on clinical and functional status in non-fibrotic HP patients (8).

Adegunsoye et al. have demonstrated that HP patients with pulmonary fibrosis treated with immunosuppressive therapy had worse baseline pulmonary functions and a higher radiological fibrosis score and long-term supplemental oxygen need. At follow-up, patients receiving immunosuppressive therapy had worsened FVC decline at 36 months compared to patients who didn't receive immunosuppressant. Evaluating 5-year survival has shown that using immunosuppressive treatment is associated with a 4.5-times greater risk of mortality compared to no treatment. However, FVC decline, mortality and transplant-free survival were similar between treatment groups (9). Even though the causative effect of systemic corticosteroid therapy on increased mortality in fibrotic HP patients is still unclear. These results are similar findings to the PANTHER-IPF trial (10, 11). These studies might suggest an early initiation of corticosteroids and the need for other therapies like anti-fibrotic medicines in severe fibrotic HP patients (6, 9).

In our study, the patients with fibrotic HP had pulmonary function loss and radiological progression more frequently. Salisbury et al. have defined 3 radiological phenotypes in HP: honeycomb, non-honeycomb fibrosis and non-fibrotic phenotypes. Radiological phenotypes are significantly related to survival and change in FVC %predicted with non-fibrotic HP patients having the best survival and improving FVC (12).

In our study, the treatment-related adverse event rate was 18.2%. Serious adverse events related to systemic corticosteroids were 8 events per 525.4 exposure months, indicating an incidence rate of 0.015 and all adverse event incidence of 0.198. These incidence rates were higher than mycophenolate mofetil and azathioprine (9).

Mycophenolate mofetil, azathioprine and rituximab are immunosuppressive agents used in the treatment of HP patients. Morisset et al. have shown a significant increase in DLCO in the first year under treatment with mycophenolate mofetil or azathioprine without a significant difference in success between the medications (13). In addition, Fiddler et al. have shown a similar effect of mycophenolate mofetil and azathioprine on DLCO in chronic HP patients (14). Evaluating factors related to azathioprine response have pointed bronchoalveolar lavage lymphocyte count, honey combing and traction bronchiectasis are associated with non-response to treatment (15). A study with small sample size showed rituximab is a safe and effective treatment option in patients with chronic HP unresponsive to corticosteroid (16).

Limitations

Sample size and the retrospective design of the study were important factors for limitation in this

study. Secondly, causative effects of prognostic factors could not be determined. Third, exposure could not be identified in some patients. Unfortunately, serum IgG testing against potential antigens associated with HP was not feasible in our institution, but the detailed history of exposure was obtained. Forth, quantitative or semi-quantitative scores for fibrosis and lung abnormalities on HRCT were not calculated. Lastly, there was not a standardized procedure for the initiation and changing of therapies, since no standard algorithm has been defined yet.

CONCLUSION

Systemic corticosteroid treatment is considered first-line treatment for HP patients, but optimal pharmacological management is still unclear. Our study suggests radiological features of fibrosis are related to a worse clinical and radiological response to corticosteroid treatment. Prospective clinical trials are needed to clarify the role of immunosuppressive therapy in HP patients.

Conflicts of interest: The authors declare that they have no conflicts of interest.

References

1. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;202(3):e36-e69. doi: 10.1164/rccm.202005-2032ST
2. Barnes H, Troy L, Lee CT, Sperling A, Strek M, Glaspole I. Hypersensitivity pneumonitis: Current concepts in pathogenesis, diagnosis, and treatment. Allergy. 2021 Jul 22. doi: 10.1111/all.15017.
3. Costabel U, Miyazaki Y, Pardo A, et al. Hypersensitivity pneumonitis. Nat Rev Dis Primers. 2020; 6 (1): 65. doi: 10.1038/s41572-020-0191-z.
4. Flaherty KR, Wells AU, Cottin V, et al. INBUILD Trial Investigators. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019; 381 (18): 1718-27. doi: 10.1056/NEJMoa1908681
5. Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia. Where We Stand and Where We Need to Go. Am J Respir Crit Care Med. 2017; 196 (6): 690-9. doi: 10.1164/rccm.201608-1675PP.
6. Ejima M, Okamoto T, Suzuki T, Anzai T, Takahashi K, Miyazaki Y. Efficacy of treatment with corticosteroids for fibrotic hypersensitivity pneumonitis: a propensity score-matched cohort analysis. BMC Pulm Med. 2021; 21 (1): 243. doi: 10.1186/s12890-021-01608-1.
7. De Sadeleer LJ, Hermans F, De Dycker E, et al. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study. Eur Respir J. 2020; 55 (4): 1901983. doi: 10.1183/13993003.01983-2019.
8. Tony FA, Soliman YMA, Salem HA. Effect of Oral Methyl Prednisolone on Different Radiological Patterns of Hypersensitivity Pneumonitis. J Asthma Allergy. 2021;14: 501-11. doi: 10.2147/JAA.S299939.
9. Adegunsoye A, Oldham JM, Fernández Pérez ER, et al. Outcomes of immunosuppressive therapy in chronic hypersensitivity pneumonitis. ERJ Open Res. 2017; 3 (3): 00016-2017. doi: 10.1183/23120541.00016-2017.
10. Idiopathic Pulmonary Fibrosis Clinical Research Network Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2093–101.
11. Idiopathic Pulmonary Fibrosis Clinical Research N Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012; 366: 1968–77.
12. Salisbury ML, Gu T, Murray S, et al. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest. 2019; 155 (4): 699-711. doi: 10.1016/j.chest.2018.08.1076.
13. Morisset J, Johannson KA, Vittinghoff E, et al. Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis. Chest. 2017; 151 (3): 619-25. doi: 10.1016/j.chest.2016.10.029.
14. Fiddler CA, Simler N, Thillai M, Parfrey H. Use of mycophenolate mofetil and azathioprine for the treatment of chronic hypersensitivity pneumonitis-A single-centre experience. Clin Respir J. 2019; 13 (12): 791-4. doi: 10.1111/crj.13086.
15. Raimundo S, Pimenta AC, Cruz-Martins N, et al. Insights on chronic hypersensitivity pneumonitis' treatment: Factors associated with a favourable response to azathioprine. Life Sci. 2021;272:119274. doi: 10.1016/j.lfs.2021.119274.
16. Ferreira M, Borie R, Crestani B, et al.Efficacy and safety of rituximab in patients with chronic hypersensitivity pneumonitis (cHP): A retrospective, multicentric, observational study. Respir Med. 2020; 172: 106146. doi: 10.1016/j.rmed.2020.106146