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A prospective observational evaluation of treatment outcomes of patients with chronic obstructive pulmonary disease and peripheral blood eosinophilia

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ABSTRACT

A prospective observational evaluation of treatment outcomes of patients with chronic obstructive pulmonary disease and peripheral blood eosinophilia

Introduction: This study aimed to compare two groups of patients with Chronic Obstructive Lung Disease (COPD) and blood eosinophil values of ≥ 300 cells/ μ L. The patients were followed up for one year in two groups, one receiving inhaled corticosteroids (ICS) and the other not receiving ICS in terms of exacerbation rates, the incidence of pneumonia, mortality rates, FEV₁, FVC and FEF₂₅₋₇₅ changes, the COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores.

Materials and Methods: Stable patients, who presented to the University Medical Faculty Chest diseases outpatient clinic and diagnosed with COPD according to pulmonary function test results and GOLD stages 2-4 according to the 2017 GOLD criteria and with blood eosinophil counts of ≥ 300 cells/ μ L were included in the study.

Results: 85 patients were included in the study, of which 76.5% (n= 65) were males. There were no significant differences between the 38 patients receiving ICS and the 47 patients not receiving ICS regarding baseline FEV₁, FVC, FEF₂₅₋₇₅ absolute values and percentages, and FEV₁, FVC values controlled at month six and month 12, and FEF₂₅₋₇₅ absolute values and percentages at month six (p> 0.05). However, the difference between the baseline and month 12 absolute values and percentages of FEF₂₅₋₇₅ was statistically significant, and the decrease from baseline was greater in the group receiving ICS (p< 0.05). The difference in CAT and mMRC scores were statistically significant at month six and month nine in favor of the group receiving ICS (p< 0.05). The median

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number of moderate and severe exacerbations were both one (min: 0, max:3) in the group receiving ICS (n= 38) and in the one not receiving ICS (n= 47). The difference of exacerbation rates in both groups were not statistically significant ($p > 0.05$).

Conclusion: In this study, it was determined that exacerbation rates of eosinophilic COPD patients did not differ depending on the use of ICS in a one-year period. Nevertheless, the 12-month FEF_{25-75} values of patients not using ICS were lower to a lesser extent, while the CAT and mMRC scores improved in favor of ICS users at different months in the one-year follow-up.

Key words: COPD; eosinophilia; exacerbation

ÖZ

Kronik obstrüktif akciğer hastalığı ve periferik kan eozinofili olan hastaların tedavi sonuçlarının prospektif gözlemsel değerlendirilmesi

Giriş: Bu çalışmanın amacı; KOAH'ı ve kan eozinofil değerinin ≥ 300 hücre/ μ L olan hastaların iki gruba ayrılarak inhaler kortikosteroid (İKS) alan ve almayan olarak 1 yıl boyunca takip edilmesi ile, alevlenme oranı, pnömoni sıklığı, mortalite, CAT, mMRC skoru, FEV_1 , FVC ve FEF_{25-75} değişimini karşılaştırmaktır.

Materyal ve Metod: Erciyes Üniversitesi Tıp Fakültesi Göğüs Hastalıkları polikliniğine başvuran, solunum fonksiyon testi bulguları ve GOLD 2017 kriterlerine göre KOAH tanısı alan, GOLD grade 2-4 olan ve kan eozinofili değeri ≥ 300 hücre/ μ L olan stabil hastalar çalışmaya alındı.

Bulgular: Çalışmaya 85 hasta alındı ve bunların %76,5'i (n= 65) erkekti. İKS alan 38 hasta ve almayan 47 hasta grubu arasında başlangıç FEV_1 , FVC, FEF_{25-75} mutlak değer ve yüzdesi ile kontrol edilen 6. ay ve 12. ay FEV_1 , FVC ve 6. ay FEF_{25-75} mutlak ve yüzde değeri arasında istatistiksel anlamlı fark izlenmemiştir ($p > 0,05$). Başlangıç FEF_{25-75} mutlak değer ve yüzdesi ile kontrol edilen 12. ay değerler arasında istatistiksel olarak anlamlı fark olup başlangıç değerine göre İKS alan grupta İKS almayan gruba göre daha fazla azalma mevcuttur ($p < 0,05$). CAT ve mMRC skoru farkı 6. ve 9. ayda İKS alan grup lehine istatistiksel olarak anlamlıdır ($p < 0,05$). Hem İKS alan grupta hem de İKS almayan grupta ortalama ağır ve orta alevlenme sayısı 1 (min= 0, max= 3) idi. İki grup arasındaki alevlenme sayısı istatistiksel olarak anlamlı değildi ($p > 0,05$).

Sonuç: Sonuç olarak bu çalışma ile eozinofilik KOAH hastalarının bir yıllık süre zarfında İKS kullanıp kullanmamasına göre alevlenme sıklığının değişmediği saptanmıştır. Bununla beraber İKS kullanmayan hastaların 12. ayda FEF_{25-75} değeri daha az düşerken, CAT ve mMRC skorlarının 1 yıllık takipteki farklı aylarda İKS kullanan hastalar lehine iyileştiği görülmüştür.

Anahtar kelimeler: KOAH; eozinofili; alevlenme

INTRODUCTION

According to WHO estimates, 65 million people have moderate to severe chronic obstructive pulmonary disease (COPD). Estimates show that COPD will become the third leading cause of death worldwide by 2030 (1). After COPD is diagnosed, effective management should be based on an individualized assessment in order to decrease both the present symptoms and risk of future exacerbations. An individualized approach is recommended to start and increase/decrease the treatment of the patient depending on the level of symptoms, and exacerbation risk (2). Continuous follow-up should include continuous assessment of exposure to risk factors and monitoring disease progression, effects and possible adverse effects of treatment, history of exacerbations and comorbidities (2). Therefore, long-term management of COPD over the years is planned not only according to the stages of the disease but also according to phenotype.

Eosinophils are cells capable of digesting bacteria, fungi, inert particles, and antigen-antibody complexes, which show their effects by releasing cellular contents (3). Presence of 250-1500/ mm^3 eosinophils in peripheral blood is considered mild eosinophilia, while presence of 1500-5000/ mm^3 and $>5000/\text{mm}^3$ are considered moderate and severe eosinophilia, respectively (4). The treatment of eosinophilic COPD is not entirely clear. Several recent studies have shown the inhibitory effect of inhaled corticosteroid (ICS) (added to regular maintenance bronchodilator therapy) on future exacerbations by monitoring blood eosinophil counts (5-10). The therapeutic effect of ICS containing regimens [ICS + long-acting muscarinic receptor antagonist (LAMA) + long-acting β -agonist (LABA)] are superior to LABA + LAMA on hospitalization in patients who had at least one exacerbation in the previous year (7). In another study, eosinophil counts were compared among LABA+LAMA combination and ICS+LABA combination. LABA+LAMA provides superior or similar benefits over salmeterol/

fluticasone regardless of blood eosinophil levels in patients with COPD (11). The differences between the studies suggest that more data is needed in this group of patients.

Therefore, we aimed to separate COPD patients with blood eosinophil counts ≥ 300 cells/ μ L into two groups as those receiving and not receiving ICS, to find the rates of exacerbations, pneumonia incidence, and mortality during a one-year follow-up and to compare the COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores, changes in FEV₁, FVC and FEF₂₅₋₇₅ values.

MATERIALS and METHODS

Patient Selection

Stable COPD patients aged above 40 years, smoking at least 10 packs/year cigarettes or with biomass exposures who presented to the Chest Diseases outpatient clinic at the University Medical Faculty and who were diagnosed with COPD according to pulmonary function test results (FEV₁/FVC values below 0.7 post-bronchodilator and negative reversibility ($>12\%$ or >200 ml improvement in FEV₁ measured after 400 μ g salbutamol inhalation) and the GOLD 2017 criteria. Those who were GOLD stages 2-4 and had blood eosinophil counts ≥ 300 cells/ μ L were included into the study between January 2018 to July 2019 (12). Patients who concomitantly had asthma, eosinophilia-causing vasculitis, Loeffler's syndrome, allergic bronchopulmonary aspergillosis, parasitic diseases, exacerbations within the last four weeks and who used oral steroids in the last four weeks were excluded from the study. Approval was obtained from the Ethics Committee of Erciyes University Medical Faculty before the study (Ethics committee consent no: 2017-453). Each patient included in the study signed a patient informed consent form explaining in detail the procedures to be performed during the study (Supplement 1- study group consent form).

The patients were separated into two groups according to the use of inhaled corticosteroids or not: Group 1 (n= 38) comprised patients using inhaled corticosteroids (receiving ICS) and Group 2 (n= 47) patients not using inhaled corticosteroids (not receiving ICS). The daily ICS regimens were budesonide 640 mcg or 800 mcg, fluticasone propionate 1000 mcg, beclomethasone dipropionate 400 mcg and fluticasone furoate 100 mcg. Treatment of the patients was planned by the physicians at the outpatient clinic,

and there was no intervention for the treatment on our side. The patients were prospectively observed for one year. Their PFT values, hemogram values, CAT scores, mMRC scores, number of exacerbations and histories were inquired and recorded at baseline. Three months later, CAT scores, mMRC scores, number of exacerbations, and mortality were inquired and recorded via phone calls. At the six-month control visit, PFT values, hemogram values, CAT scores, mMRC scores, number of exacerbations and mortality were inquired and recorded. At month nine, CAT scores, mMRC scores, number of exacerbations and deaths were inquired via phone calls and recorded. At the 12-month control, PFT values, hemogram values, CAT scores, mMRC scores, number of exacerbations and mortality were inquired and recorded.

Moderate and severe exacerbations were recorded. Moderate exacerbation was defined as the condition where the patient was treated (short-acting β_2 agonists) SABAs plus antibiotics and/or oral corticosteroids. In contrast, a severe exacerbation was defined as the condition where the patient required hospitalization or visits to the emergency room (12). Severe exacerbations may also be associated with acute respiratory failure. Pneumonia was diagnosed according to clinical and radiological criteria.

Assessment of Comorbidities

The comorbidities of the patients were asked and recorded.

Evaluation of CAT and mMRC Scores

A questionnaire including questions about CAT and mMRC was applied to the patients, and the total score was recorded.

Pulmonary Function Test

Pulmonary function tests were performed at the Erciyes University Medical Faculty Chest Diseases outpatient clinic by trained and experienced respiratory function test technicians of at least five years using a Vmax 20c spirometer device while the patients were in a sitting position. Following at least three maneuvers of the pulmonary function test, the best result was recorded. At baseline, the first PFT was performed with bronchodilators to rule out the diagnosis of asthma, and another PFT (without bronchodilators) was performed in the sixth and 12th month. Patients diagnosed with COPD were separated into groups A, B, C and D according to GOLD 2017 criteria and CAT, mMRC scores, number of

attacks and history of hospitalizations were recorded (12).

Hemogram

According to the results of the hemogram studied at the central laboratory of Erciyes University Medical Faculty Hospital, patients' white blood cell counts, hemoglobin, eosinophil percentages, and absolute values at baseline, and sixth and 12th months were recorded.

Statistical Analysis

SPSS software (Statistical Package for the Social Sciences, 22.0 version; SSPS Inc., Chicago, Illinois, USA) was used for statistical analysis. The distribution of continuous variables was tested with one-sample Kolmogorov-Smirnov Test; data were given as mean value $\pm$ standard deviation or median, minimum-maximum ranges. Categorical variables were reported as frequency and group percentages. For the comparison of two groups, Student's t-test was used for parametric values, and the Mann-Whitney U-test was used for non-parametric values. The categorical variables were analyzed with the chi-square test. For

comparisons of more than two groups, One-way ANOVA was used for parametric values and the Kruskal Wallis-Variance Analysis for non-parametric values. Exacerbation rates were analyzed by Mann-Whitney U test and exacerbation percentages were analyzed by Pearson chi square test. All p values were two-sided, and p values below 0.05 were considered significant.

RESULTS

85 patients with a mean age of 63.3 ± 9.7 years were included in the study. Of the patients, 76.5% (n= 65) were males. Mean absolute eosinophil counts and percentages were 428.7 ± 130.9 $10^3/\text{ml}$ and $5.1 \pm 1.4\%$, respectively. Mean FEV₁ values and percentages of the patients were 1886.4 ± 658.1 ml and $68 \pm 20\%$, respectively. The inhaler therapies received by the patients, according to COPD groups, are given in the supplementary material. While 38 patients received (44.7%) ICS, 47 (55.3%) did not. There were no significant differences between the groups with and without ICS regarding sex, age, eosinophil counts, PFT parameters, and dyspnea scores ($p > 0.05$) (Table 1). The most frequent comorbidities were

Table 1. Comparison of both groups of patients included in the study in terms of age, smoking status, hemogram, blood eosinophil counts and PFT value

Variables	Total (n= 85) (mean $\pm$ SD)	Group 1: with ICS n= 38 (mean $\pm$ SD)	Group 2: without ICS (n= 47) (mean $\pm$ SD)	p
Sex (M/F)	65/20	27/11	38/9	>0.05
Age (years)	63.3 ± 9.7	61.4 ± 10.8	64.7 ± 8.5	>0.05
Smoking (packs)	41.2 ± 22.5	38.6 ± 24.6	43.2 ± 20.7	>0.05
White cell count	8160.2 ± 1765.8	8371.2 ± 1796.9	7989.6 ± 1740.7	>0.05
Hemoglobin (gr/dl)	14.9 ± 1.81	15.5 ± 2	14.7 ± 1.6	>0.05
Eosinophil absolute ($10^3/\text{mL}$)	428.7 ± 130.9	418.4 ± 124.4	437 ± 136.7	>0.05
% Eosinophil	5.1 ± 1.4	5 ± 1.4	5.2 ± 1.4	>0.05
FEV ₁ /FVC	59.3 ± 8.7	58.9 ± 9.6	59.5 ± 8	>0.05
FEV ₁ (mL)	1886.4 ± 658.1	1886.5 ± 731.3	1886.3 ± 600.6	>0.05
%FEV ₁	68 ± 20	67.2 ± 21.9	68.7 ± 18.6	>0.05
FVC (mL)	3120.2 ± 895.3	3127.8 ± 1000	3114 ± 811.8	>0.05
%FVC	87.7 ± 20.1	86.3 ± 22.9	88.9 ± 17.7	>0.05
FEF ₂₅₋₇₅ (L/sn)	963.4 ± 456	1003.4 ± 483.6	931 ± 434.9	>0.05
%FEF ₂₅₋₇₅	31.3 ± 13.8	31.3 ± 13.4	31 ± 14.3	>0.05
Cat	10 (1-28)	11 (2-28)	10 (1-24)	>0.05
MMRC	1 (0-4)	1 (0-3)	1 (0-2)	>0.05

ICS:Inhaled corticosteroid, PFT: Pulmonary function test, M: Male, F: Female, CAT: Chronic obstructive lung disease assessment test, mMRC: Modified medical research council.

Table 2. Comorbidities and their frequency in patients included in the study

	Total n= 85	%
Patients with comorbidities	77	90.6
Hypertension	43	50.6
Diabetes mellitus	24	28.2
Coronary artery disease	22	25.9
Chronic renal failure	8	9.4
Malignancy	5	5.9
Rheumatoid arthritis	3	3.5
Congestive heart failure	3	3.5
Obstructive sleep apnea	2	2.3
No comorbidities	8	9.4

diabetes mellitus and hypertension, and there was not statistically difference between comorbidities in patients receiving ICS and not receiving ICS ($p > 0.05$) (Table 2).

Regardless of the treatment received, 29.4% ($n = 25$) of 85 patients included in the study were in Group A, 38.9% ($n = 33$) were in Group B, 16.5% ($n = 14$) were in Group C, and 15.3% ($n = 13$) were in Group D. There was no significant difference between the eosinophil absolute values and percentages of the COPD patients in Groups A, B, C and D; A $473.6 \pm 151.2 \text{ } 10^3/\text{mL}$ ($5.3 \pm 1.2\%$); B $427.8 \pm 126.7 \text{ } 10^3/\text{mL}$ ($5.3 \pm 1.5\%$); C $378.5 \pm 95.9 \text{ } 10^3/\text{mL}$ ($4.8 \pm 1.3\%$); D $398 \pm 115.6 \text{ } 10^3/\text{mL}$ ($4.6 \pm 1.5\%$); $p > 0.05$. The distribution of inhaler treatments received by patients according to COPD stages and the COPD groups of patients receiving and not receiving ICS are shown in Supplementary Table 1 and 2.

Median number of moderate and severe exacerbations were both one (min= 0, max= 3) in the group receiving ICS ($n = 38$) and also in the group not receiving ICS ($n = 47$). The difference in exacerbation rates in both groups was not statistically significant

($p > 0.05$) (Table 3). There were 6 (15.8%) cases of pneumonia in the group receiving ICS and also 6 (12.8%) pneumonia cases in the group not receiving ICS ($p > 0.05$). Two patients in the group not receiving ICS died in the first three-month period of the follow-up while no other deaths were recorded in the group receiving ICS (mortality 4.2% in the group not receiving ICS and 2.3% in total patients included in the study).

There was no statistically significant difference between baseline FEV_1 and FVC absolute values and the FEV_1 absolute values controlled in the 6th and 12th months of the patients included in the study receiving and not receiving ICS ($p > 0.05$). Again, there was no significant difference between baseline FEF_{25-75} absolute values and percentages, and the values controlled in the 6th month ($p > 0.05$). However, there was a significant difference between the FEF_{25-75} absolute values and the values controlled in the 12th month. The decrease from baseline was greater in the group receiving ICS ($-114.9 \pm 228.2 \text{ mL}$ in the ICS group and $-87.1 \pm 241.7 \text{ mL}$ in the non-ICS group) ($p < 0.05$) (Table 4).

Table 3. Numbers of exacerbations in the groups receiving and not receiving ICS

Number of exacerbations	Group 1: with ICS n= 38 (%)	Group 2: without ICS n= 47 (%)	p
0	10 (26.3%)	9 (19.1%)	>0.05
1	15 (39.5%)	22 (46.8%)	
2	8 (21.1%)	13 (27.7%)	
3	5 (13.2%)	3 (6.4%)	

ICS: Inhaled corticosteroid.

Table 4. Comparison between baseline FEV₁, FVC and FEF₂₅₋₇₅ values and the 6th and 12th-month values in groups receiving and not receiving ICS

PFT findings	Group 1: with ICS (n= 38)	Group 2: without ICS (n= 45)	p
FEV ₁ difference at month 6	-42.1 ± 222.8	-79.7 ± 187.5	>0.05
FEV ₁ difference at month 12	-85.2 ± 270.2	-141.7 ± 232.3	>0.05
FVC difference at month 6	-100.8 ± 326.4	-116.6 ± 256.5	>0.05
FVC difference at month 12	-172 ± 345.2	-122.8 ± 350.2	>0.05
FEF ₂₅₋₇₅ difference at month 6	-75 ± 180.4	-48 ± 200	>0.05
FEF ₂₅₋₇₅ difference at month 12	-114.9 ± 228.2	-87.1 ± 241.7	<0.05

PFT: Pulmonary function test, ICS: Inhaled corticosteroids.

Table 5. The CAT, mMRC scores and differences in 3, 6, 9 and 12 months of patients receiving and not receiving ICS

Variables	Receiving ICS (n= 38) Median (min/max)	Not receiving ICS (n= 45) Median (min/max)	p
CAT 3 rd month	0 (-7/3)	0 (-6/5)	>0.05
CAT 6 th month	-1 (-11/6)	0 (-11/6)	<0.05
CAT 9 rd month	-1 (-13/10)	1 (-10/8)	<0.05
CAT 12 th month	-1 (-10/7)	0 (-12/4)	>0.05
mMRC 3 rd month	0 (-1/2)	0 (-1/1)	>0.05
mMRC 6 th month	0 (-2/1)	0 (-1/1)	<0.05
mMRC 9 rd month	0 (-2/2)	0 (-1/1)	<0.05
mMRC 12 th month	0 (-2/2)	0 (-2/1)	>0.05

CAT: Chronic obstructive pulmonary disease assessment test, mMRC: Modified medical research council, ICS: Inhaled corticosteroid.

In groups receiving and not receiving ICS, median (min/max) differences in CAT were -1 (-11/6) and 0 (-11/6) in the sixth month, and -1 (-13/10) and 1 (-10/8) in the ninth month; on the other hand, median (min/max) differences in mMRC were 0 (-2/1), 0 (-1/1) in the sixth month and 0 (-2/2), 0 (-2/1) in the ninth month ($p < 0.05$) (Table 5). Again, the differences in CAT and mMRC scores continued to decrease less in the 12th month, but the difference was not significant ($p > 0.05$).

Comparison of both groups in terms of PFT values, CAT, and mMRC scores of patients in COPD stages B, D are given in the supplemental material (Supplementary Tables 3-5).

DISCUSSION

In this study, the patients diagnosed with COPD and blood eosinophil counts ≥ 300 cells/ μ L were separated into two groups independent of the stage (those receiving and not receiving ICS), followed up for one

year. No significant difference was found among them regarding the number of exacerbations, incidence of pneumonia, and decreases in FEV₁ and FVC values. However, the FEF₂₅₋₇₅ values yielded significant results in favor of the group not receiving ICS in the 12-month follow-up, and CAT and mMRC scores in favor of the group receiving ICS at certain months during follow-up. Two patients died in the non-ICS receiving group during the study and there was no mortality in the ICS receiving group.

The effect of blood eosinophil values on the rates of hospitalization for COPD exacerbation is still not clear. However, some retrospective and post-hoc analyses have revealed a relationship between higher rates of exacerbation and higher blood eosinophil counts, while other studies have noted lower rates of hospitalizations and exacerbations in COPD patients with high eosinophil levels (13-15). In the subgroup analyses of the FLAME study where the differences in the efficacies of ICS/LABA and LABA/LAMA in the

prevention of exacerbations were analyzed according to blood eosinophil values during one year, fewer exacerbations were noted in favor of patients receiving LABA/LAMA therapy in groups with eosinophil values <2%, 2-3%, 3-5% and counts <150 cells/ μ L (11). In a study comparing combination therapies of ICS/LABA and LABA/LAMA according to eosinophil percentages in COPD patients grouped as <2% and $\geq$ 2%, ICS/LABA combination has been found to be more efficient in the prevention of exacerbations in a follow-up longer than one year in patients with eosinophil levels $\geq$ 2% (16). In another randomized controlled study with similar results, ICS/LABA therapy has been found to be more effective than LABA therapy alone in the reduction of exacerbations in patients with blood eosinophil levels higher than 2.4% (17). Again, in another study comparing a triple treatment including ICS with a dual treatment not including ICS, the number of exacerbations was significantly reduced in favor of the group using ICS in patients with eosinophil levels higher than 2% (8). In our study, on the other hand, there was no significant difference between the groups receiving and not receiving ICS in terms of exacerbations in eosinophilic COPD patients. Our data also provide a different contribution to the literature, which includes contradictory data on this subject.

Also, some studies have found that ICS use increases pneumonia risk in COPD (18). In a recently performed network analysis, ICS use was shown to increase pneumonia risk in COPD patients with eosinophil counts below 100/ μ L and chronic bacterial infection (19). However, in the study by Pavord et al., ICS has not been shown to increase pneumonia risk, especially in COPD patients with eosinophilia levels greater than 2% (20). Again in our study, there was no significant increase in pneumonia incidence in patients using ICS in support of the literature because COPD patients with eosinophil counts above 300/ μ L were included in the study. This may be explained by the behavior of eosinophilic COPD patients as asthma.

The CAT and mMRC scores are used in the follow-up and staging of COPD patients (2). In a population-based study evaluating the efficiency of the CAT test in the assessment of COPD, 404 cases diagnosed with COPD among 6600 adults were evaluated (21). According to this study, the CAT score was found to determine the severity of symptoms better than mMRC. However, mMRC is used more frequently in

daily practice because it is more practical. When the CAT and mMRC scores of COPD patients in our study were analyzed, a significant difference was noted, especially in the 6th and 9th months. Nevertheless, when the difference in CAT and mMRC scores were compared among COPD stages of B and D in the 3rd, 6th, 9th, and 12th months, the difference in CAT and mMRC scores was found to be significant in the 6th month. This shows that the decrease in the severity of symptoms is seen prominently in the sixth month according to CAT and mMRC among symptomatic low (B) and high (D) risk stages. However, in a study, the total scores of St George's Respiratory Questionnaire (SGRQ) and the Transition Dyspnea Index in the 52nd week improved more in patients using ICS and with eosinophil counts above 310 compared with the patients not using ICS (22). Whereas, in the subgroup analysis of the FLAME study, there was no significant difference in the SGRQ-C questionnaire scores of the patients with eosinophilia of greater than 2% between those who received ICS and those who did not (11).

There was no significant difference between baseline FEV₁ absolute values and percentages and the FEV₁ absolute values and percentages in the 6th and 12th month controls in the patients who did and did not receive ICS. However, FEV₂₅₋₇₅ value was found to be significantly more reduced in the 12th month in the group receiving ICS. These results show that the small airways did not get better in patients receiving ICS. However, there are confusing results in the PFT parameters in the literature about receiving ICS or not receiving ICS in patients with eosinophilic COPD. In a study comparing indacaterol/glycopyrronium with salmeterol + fluticasone, on the other hand, 52-week FEV₁ loss was in favor of the patients not receiving ICS both in the patient group with eosinophil counts less than 2% and in the patient group with eosinophil counts greater than 2% (11). Nevertheless, in the analysis of the IMPACT study, it has been found that when patients with eosinophil counts above 310 used ICS, the loss in FEV₁ was less (22). There are different results in different studies about pulmonary function test parameters in eosinophilic patients with ICS containing therapeutic regimens, and research will be continued on this subject in the future.

Different distinguishing data other than exacerbation and dyspnea scales are needed for planning therapy in COPD cases. Although eosinophil counts are one of them, many different studies with many patients

yield different results. Perhaps a meta-analysis of these studies may provide benefit for this controversial subject.

As a limitation, the number of patients remained below our target. So, when we divided patients into four groups, such as COPD stages A, B, C, and D, the subgroups did not contain enough patients to compare within themselves. In addition, we did not divide the patients with moderate or severe exacerbations. So, we did not compare the groups with only moderate or severe exacerbations.

In conclusion, it was found in this study that the frequency of exacerbations did not differ depending on ICS use during the one-year follow-up in eosinophilic COPD patients. However, two patients died in the non-ICS group, and there was no mortality in ICS receiving group. Nevertheless, the FEF₂₅₋₇₅ values of the patients not receiving ICS were better in the 12th month, while CAT and mMRC scores improved in favor of the patients using ICS at different months during the one-year follow-up. This subject, which has still not been clarified, should be investigated with more studies.

Ethical Committee Approval: This study approval was obtained from Erciyes University Faculty of Medicine Ethics Committee (Decision No: 2017/453).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: NT, İG, FSO

Analysis/Interpretation: FA, BBK

Data acquisition: FA

Writing: NT, İY

Clinical Revision: NT, BBK

Final Approval: FA

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