doi • 10.5578/tt.20219905
Tuberk Toraks 2021;69(1):39-48
Geliş Tarihi/Received: 22.02.2021 • Kabul Ediliş Tarihi/Accepted: 18.03.2021

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

The significance of eosinophil and eosinophil lymphocyte ratio (ELR) in predicting response to omalizumab treatment in patients with severe allergic asthma

Hasan ÖZGEN[1](ID)
Fatma Merve TEPETAM[2](ID)
İsmet BULUT[2](ID)
Cihan ÖRÇEN[3](ID)

[1] Clinic of Chest Diseases, Bartın State Hospital, Bartın, Turkey
[1] *Bartın Devlet Hastanesi, Göğüs Hastalıkları Kliniği, Bartın, Türkiye*
[2] Department of Immunology and Allergy, University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2] *Sağlık Bilimleri Üniversitesi, Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, İmmünoloji ve Alerji Anabilim Dalı, İstanbul, Türkiye*
[3] Clinic of Chest Diseases, University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey
[3] *Sağlık Bilimleri Üniversitesi, Derince Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Kocaeli, Türkiye*

Cite this article as: *Özgen H, Tepetam FM, Bulut İ, Örçen C. The significance of eosinophil and eosinophil lymphocyte ratio (ELR) in predicting response to omalizumab treatment in patients with severe allergic asthma. Tuberk Toraks 2021;69(1):39-48.*

Yazışma Adresi (Address for Correspondence)
Dr. Hasan ÖZGEN
Bartın Devlet Hastanesi,
Göğüs Hastalıkları Kliniği,
BARTIN - TÜRKİYE
e-mail: hasankiozgen@gmail.com

ABSTRACT

The significance of eosinophil and eosinophil lymphocyte ratio (ELR) in predicting response to omalizumab treatment in patients with severe allergic asthma

Introduction: *Th2/Th1 mix pathological pathway may be seen as a common set of low eosinophilic phenotype in severe allergic asthma. This may affect omalizumab treatment response. In our study, we aimed to investigate whether eosinophil count (EOS) and percentage (EOS%), eosinophil lymphocyte ratio (ELR) and neutrophil lymphocyte ratio (NLR) may predict omalizumab treatment.*

Materials and Methods: *Patients who received omalizumab treatment at least for one year in our allergy clinic were screened retrospectively. Baseline hemogram parameters, pre- and post-treatment emergency admissions, annual attacks requiring steroid use, hospitalizations, spirometric changes, and asthma control tests (ACT) were recorded. According the global efficacy assessment (phisician's GETE) scale patients was recorded as responder and nonresponder. By looking at EOS, EOS%, ELR and NLR distributions in these groups, the role of these parameters in representation of the treatment efficacy was investigated.*

Results: *The study was carried out with 83 patients, 77.1% of whom were women with an average age of 50.03 ± 10.7. While ACT scores and* FEV_1,

FEF_{25-75} was significantly increased, the number of emergency admissions, annual attacks and hospitalizations decreased significantly ($p< 0.05$). The rate of patients signed as responder was 75.9%, while the rate of nonresponder was %24.1. When the two groups were compared, it was found that the EOS, EOS% and ELR were significantly higher in the responder group. The cut-off values according to the ROC curve were determined as 0.12, 310/ml and 3.1% respectively. Considering the sensitivity (58.73%); specificity (85.00%); positive predictive value (92.50%), it was determined that ELR was a more valuable test.

Conclusion: *Instead of expensive and invasive methods for predicting the response of omalizumab therapy in severe allergic asthma, the ELR is correlated with treatment response and giving hope to be easier way to reach.*

Key words: *Eosinophil; eosinophil lymphocyte ratio; omalizumab*

ÖZ

Ağır alerjik astımı olan hastalarda omalizumab tedavi yanıtı öngörmede eozinofil ve eozinofil lenfosit oranının (ELR) önemi

Giriş: *Ağır alerjik astımda, düşük eozinofilik fenotipin ortak alt küme olarak bulunabilmesi nedeniyle, Th2/Th1 karışım patolojik yolağı görülebilir. Bu durum omalizumab tedavisinin yanıtını etkileyebilir. Çalışmamızda eozinofil sayısının (EOS) ve yüzdesinin (EOS%), eozinofil lenfosit oranının (ELR) ve nötrofil lenfosit oranının (NLO) omalizumab tedavi yanıtını öngörmedeki yerini belirlemeyi amaçladık.*

Materyal ve Metod: *Alerji kliniğimizde en az bir yıl omalizumab tedavisi alan hastalar retrospektif olarak tarandı. Başlangıç hemogram parametreleri, tedavi öncesi ve sonrası acil başvurular, steroid kullanımı gerektiren yıllık ataklar, hastaneye yatışlar, spirometrik değişiklikler ve astım kontrol testleri (ACT) kaydedildi. Global etkinlik değerlendirme (GETE) ölçeğine göre hastalar yanıt alınan ve yanıt alınamayan olarak kaydedildi. Bu gruplarda EOS, EOS%, ELR ve NLR dağılımlarına bakılarak, bu parametrelerin tedavi etkinliğini temsil etmedeki rolü araştırıldı.*

Bulgular: *Çalışma, yaş ortalaması 50,03 ± 10,7 olan %77,1'i kadın 83 hasta ile gerçekleştirildi. ACT puanları ve FEV_1, FEF_{25-75} anlamlı olarak artarken, acil başvuru, yıllık atak sayısı ve hastaneye yatış sayısı anlamlı olarak azaldı ($p< 0,05$). Tedavi yanıtı alınan hasta oranı %75,9, yanıt alınmayanların oranı ise %24,1 idi. İki grup karşılaştırıldığında, yanıt veren grupta EOS, EOS% ve ELR'nin anlamlı olarak daha yüksek olduğu bulundu. ROC eğrisine göre kestirim değerleri sırasıyla 0,12, 310/ml ve %3,1 olarak belirlendi. Sensitivite (%58,73); spesifite (%85,00); pozitif prediktif değerler (%92,50), göz önüne alındığında ELR'nin daha değerli bir test olduğu belirlenmiştir.*

Sonuç: *Ağır alerjik astımda omalizumab tedavi yanıtını öngörmek için pahalı ve invaziv yöntemler yerine, tedavi yanıtıyla korelasyon gösteren ELR ulaşılabilirliği kolay bir test olarak umut vaat etmektedir.*

Anahtar kelimeler: *Eozinofil; eozinofil lenfosit oranı; omalizumab*

INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways and bronchial hyperreactivity. It is defined by a variable airflow obstruction as well as variation of respiratory symptoms over time and in intensity, such as wheezing, shortness of breath, chest tightness, and cough (1) With the determination of the role of inflammation in the pathogenesis of the disease, steroids have formed the basis of treatment.

Eosinophil and lymphocyte accumulations in the airway mucosa of untreated patients were detected, and the decrease in these cells with inhaled corticosteroids (ICS) revealed improvement in respiratory functions, and later studies revealed that this type of inflammation was not the same in every patient (2). According to the predominant cell type, three different inflammatory asthma phenotypes have been described, mainly eosinophilic, neutrophilic and pauci-granulocytic asthma. These three types are thought to have different clinical and treatment response characteristics (2,3). Despite the significant clinical success of inhaled corticosteroids, leukotriene regulators and combined ICS and □2-agonists, the burden of particularly severe asthma continues to increase. Recently, many biological agents that may be effective in asthma treatment have been investigated. Some of these new agents are still in preclinical or early development stages. Biological agents targeting the Th2 pathway such as omalizumab, mepolizumab, dupilumab, reslizumab, and benralizumab are useful in selected patient groups (4).

Mild to moderate allergic asthma is commonly characterized by Th2 cell-mediated eosinophil infiltration and remodeling. Severe asthma is characterized by the association of Th1 and Th2 cells and the collaboration of Th17 cells (5-7). In addition to eosinophils, neutrophilic airway inflammation and infiltration induced by cytokines such as TNF-a, INF-g, IL-17 and

IL-27 may accompany severe asthma. In severe allergic persistent asthma that cannot be controlled, monoclonal antibody Anti-IgE omalizumab treatment binds to the Fc part of immunoglobulin E (IgE) and prevents the activation of IgE receptors on mast cells, basophil and dendritic cell surfaces. In addition, omalizumab causes numerical decrease-down regulation of FcεRI receptors that show high affinity for IgE on the cell surface of mast cells, eosinophils and basophils. Thus, the release of inflammatory mediators that cause Type 1 IgE-mediated allergic reaction by preventing mast cell degranulation and decrease in eosinophil levels in sputum and mucosa are provided.

Researches have revealed that, omalizumab treatment significantly reduce asthma attacks in patients with peripheral basal blood eosinophil level above 260 cells/μL and in the patient population whose peripheral eosinophil level decreased by more than 50% after treatment (8,9).

However, other than eosinophilic and neutrophilic asthma, there are also patients included in the mixed phenotype, which includes both groups. This phenotype consists of patients with eosinophil level >3% and neutrophil level >60% in induced sputum (10-12).

Induced sputum examination is not very practical in determining these patient groups in the clinic and the rate of error in sample collection is high. Bronchoalveolar lavage (BAL), on the other hand, is a highly invasive procedure. However, it has been shown that the neutrophil lymphocyte ratio (NLR), which is an indicator of inflammation in chronic obstructive pulmonary disease (COPD), is associated with the severity of the disease, attacks, and mortality (13). Neutrophilic asthma is known to have similar immunological properties with COPD.

In our study, we aimed to determine the importance of markers such as eosinophil count and percentage (%), eosinophil lymphocyte ratio (ELR) and neutrophil lymphocyte ratio (NLR) in patients with eosinophilic and noneosinophilic severe allergic persistent asthma, in predicting omalizumab treatment effectiveness by using blood count, such a standard and easy-to-perform test.

MATERIALS and METHODS

In our single-center retrospective observational study, patients who started omalizumab treatment after being diagnosed with severe allergic asthma in our immunology and allergy clinic, and received omalizumab treatment for at least one year were included in the study. The data of the patients were collected from the hospital archive, the hospital automation system and by interviewing in person when necessary. Study consent was obtained from the ethics committee of our hospital.

Patients

In our study, for the patients whose asthma diagnosis was confirmed with variable respiratory symptoms and variable airflow limitation according to the criteria determined by GINA, ATS/ERS guidelines. Despite good inhaler medication compliance, correct inhaler technique application, and the optimization of concomitant diseases with treatment, asthma could not be controlled despite taking high dose ICS and a second controlling drug or, those who had asthma attacks 2 times or more in the last 1 year , requiring systemic steroid use for at least 3 days, or who had at least one history of hospitalization due to an attack were defined as severe asthma. Among these patients; the ones who were aged >18 years old, whose total Immunoglobulin E level was 30-1500 IU/mL, whose perennial allergen sensitivity is determined by specific IgE (ImmunoCap; Pharmacia Diagnostics AB, Uppsala, Sweden) or skin prick test, who have a related allergen-triggered asthma clinic and were started on Omalizumab [Xolair, Novartis-Switzerland] treatment for at least 1 year were included in the study. Patients with comorbid diseases such as malignancy, rheumatological disease, bronchiectasis, vasculitis, sarcoidosis or interstitial lung disease were excluded from the study.

Demographic characteristics of the patients, age at onset of the asthma, smoking history, the treatments they were using before omalizumab treatment, skin prick test results, comorbid diseases, body mass index (BMI), hemogram results, total immunoglobin E (IgE) levels and duration of omalizumab treatment were recorded during the treatment process. Although 142 patients examined, 83 patients could be studied due to data deficiencies or other reasons.

Effectiveness Measurements

Emergency applications before and after treatment, hospitalizations if any, and the attacks that require taking steroids for at least 3 days, asthma control test (ACT) scores, changes in pulmonary function test

(SFT) parameters were compared. The changes in each patient's controlling drugs were recorded. In evaluation of omalizumab treatment response, Global Evaluation of Treatment Effectiveness (GETE) scale was used.

The cases evaluated as excellent or good according to the GETE scale defined as the group with response, while the cases evaluated as moderate, mild or worsening were defined as the group with no response (14-19). By looking at eosinophil level, percentage, ELR and NLR distributions in these groups, the role of these parameters in representation of the treatment efficacy was investigated. If the peripheral eosinophil level in the baseline was ≥260/μL, signed as high eosinophilic, if <260/μL, it was signed as low eosinophilic group.

Statistical Analysis

Results are presented as average ± standard deviation (Standard deviation: SD) in normal distribution, and when there was no normal distribution, median and interquartile range (IQR) were used. Lung function, emergency applications, hospitalization, asthma control test (ACT) and other related variables were analyzed by calculating average or median changes before and after treatment, targeting 95% consistency and paired T-test or wilcoxon signed ranks test was used according to distribution.

When the groups with and without responses were compared, Chi-square test was used for categorical data, and if the numerical data was normally distributed, parametric test, if not, then Mann-Whitney U-test was used. ROC analysis and diagnostic screening tests were used to determine the cut-off point for ELR, EOS and EOS (%) according to benefit in the GETE asthma scale. SPSS program (SPSS Inc., IL, USA) and NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) were used for statistical analysis.

RESULTS

Our study was carried out with 83 persistent severe allergic asthmatic patients, 77.1% of whom were women with an average age of 50.03 ± 10.78, who were given omalizumab treatment for at least 1 year. The median total IgE level at baseline was 229.5 IU/mL, the man BMI was 29.42 ± 6.16 kg/m^2, the age of onset of asthma ranges from 0 to 72, the median was 28 years old. When smoking situations were examined; 66.3% (n= 55) were nonsmokers, 28 patients with a history of smoking had a median of 5 (1-40) pack years of smoking, only 3 of them were continuing active smoking. All patients were sensitized to at least 1 perennial antigen including house-dust mites, molds, cat-dog dander, and cockroach. When the most common accompanying diseases were examined, rhinosinusitis in 65.1% (n= 41), drug allergy in 25.4% (n= 16), gastroesophageal reflux (GER) in 23. 4 % (n= 15) and food allergy in 20.6% (n= 13) of the cases, had respectively. Baseline demographics and clinical characteristics are shown in Table 1.

Patients median (interquartile range) score at baseline for the ACT was 7 (4-18) points. In the last 1 year the number of emergency administiration was 22 (7-36), attacks requiring systemic steroid use at least 3 days was 3 (1-12) , and hospitalization was 1 (0-2). When we look at the pulmonary function test, the baseline mean FEV_1 was 1.69 ± 0.77 lt, PEF%: 57.64 ± 24.64, FEF_{25-75}% was 40.44 ± 28.16. When we examined the complete blood count, the basal eosinophil level was 200 /μL, ELR: 0.1 and the NLR was 2.2. For the second controlling drug during the treatment, 85.1% of the patients were using montelukast, 49.3% theophylline and 27.7% tiotropium.

After the omalizumab treatment given for a mean of 3.5 ± 1.69 years, a significant improvement was observed in the ACT of the patients. Significant reductions were observed in average emergency admissions (90%), in the number of attacks requiring systemic steroid use (81%) and in hospitalizations (85.5%). (Considering the median values, a 100% decrease was determined for all these parameters.) Not only FEV_1 but also FEF_{25-75} was increased significantly after omalizumab treatment (Table 2). A decrease in patients need for controlling medication is detected after omalizumab treatment, and these reductions were significant only for montelukast and theophylline (respectively 17.5%, p= 0.008; 60.6%, p= 0.001).

According to the GETE asthma scale, 22.8% (n= 19) of the cases improved perfectly, 53% (n= 44) significantly improved; limited improvement was observed in 14.45% (n= 12), and there was no noticeable change in 9.6% (n= 8) No cases worsening under treatment were detected. 75.9% (n= 63) of the cases were identified as the group of responder, and 24.1% (n= 20) as the group of nonresponders.

ELR, EOS and% EOS measurements of the patients in the responded group were found to be statistically and significantly higher than those who did not (p<

Table 1. Baseline demographics and patient characteristics

Age, years	50.03 ± 10.78
Female	64 (77.1)
Male	19 (22.9)
BMI kg/m^2	29.42 ± 6.16
Total IGE IU/ml	229 (91-520)
Asthma onset age,year	28 (0-72)
Smoking history	
Nonsmoker	55 (66.3)
Quitted smoking	25 (30.1)
Still smoking	3 (3.6)
Frequent Concomitant disease	
Allergic rhinosinusit	41 (65.1)
Drug allergy	16 (25.4)
Food Allergy	13 (20.6)
Gastroesophageal reflux	15 (23.4)
Allergen sensitivity	
House dust mite	66 (86.8)
Cat/dog dander	10 (13.5)/15 (20.3)
Fungus	24 (32.4)
Cockroach	16 (21.6)
Pollen	27 (36.5)

Values are expressed as n (%), mean ± SD , or median (interquartile range).

Table 2. Clinical and spirometric improvements after omalizumab treatment

	Pretreatment	Posttreatment	p
Annual emergency department visit	22 (7-36)	0 (0-2)	0.001
Annual exacerbations requiring systemic steroid at least 3 days	3 (1-12)	0 (0-1)	0.001
Annual exacerbations requiring hospitalization	1 (0-2)	0 (0-0)	0.001
ACT	7 (6-10)	20 (17-24)	0.001
FEV_1 lt	1.69 ± 0.7	1.9 ± 0.81	0.004
FEF_{25-75} (%)	29 (21-68)	48 (25-66.5)	0.006

Values are expressed as median (interquartile range) or mean ± SD.

0.05). While the rate of unresponsive patients was 25% in eosinophilic asthma, this rate was 75% in non-eosinophilic asthma (p= 0.017). Based on this significance, ROC analysis and diagnostic screening tests were used to determine the cut off point for ELR, EOS and EOS (%). The cut off point for ELR was 0.12, for EOS 310/µL, and for EOS (%)3.1% and above. Considering the sensitivity, specificity and positive predictive values, it was determined that ELR was a more valuable test (Table 3). For the ELR 0.12 predictive value; sensitivity 58.73%; specificity 85.00%; positive predictive value is 92.50% and negative predictive value is 39.53%. The area under the obtained ROC curve was 67.9% and standard error was 6.0% (Figure 1).

As shown in Figure 2, when examining the relationship between the benefit from omalizumab treatment and the cut off values of ELR, EOS and EOS (%), the rate of benefit in cases with ELR level 0.12≤ is 8 times [ODDS rate for ELR is 8.064 (%95 CI: 2.142-

Table 3. Diagnostic Screening Tests and ROC Curve Results for ELR, EOS and EOS (%)

	Diagnostic Scan			ROC Curve				p
	Cut off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	
ELR	**0.12**	58.73	85.00	92.50	39.53	**0.679**	0.562-0.796	**0.017**
EOS (cell/□L)	**≥310**	47.62	85.00	90.91	34.00	**0.650**	0.519-0.781	**0.04**
EOS (%)	**≥3.1**	58.73	75.00	88.10	36.59	**0.678**	0.550-0.806	**0.017**

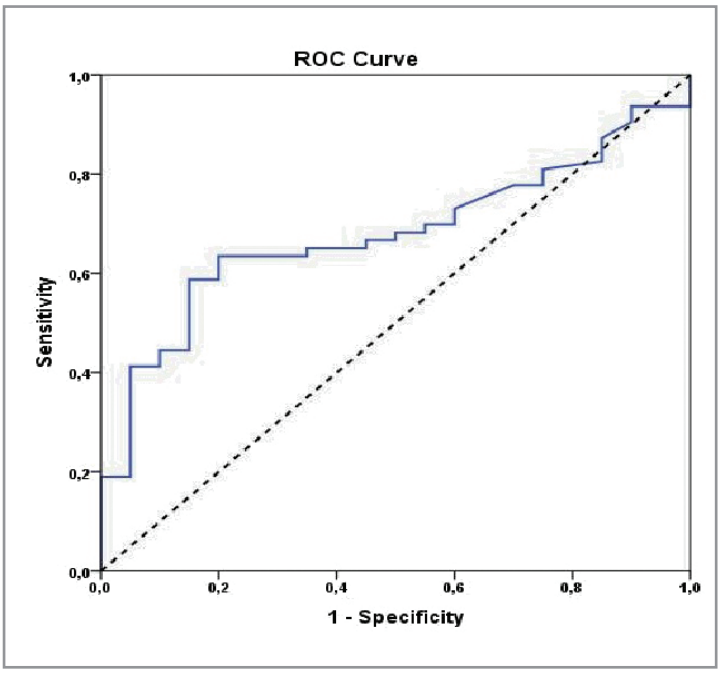

Figure 1. ROC curve for ELR level according to benefit status.

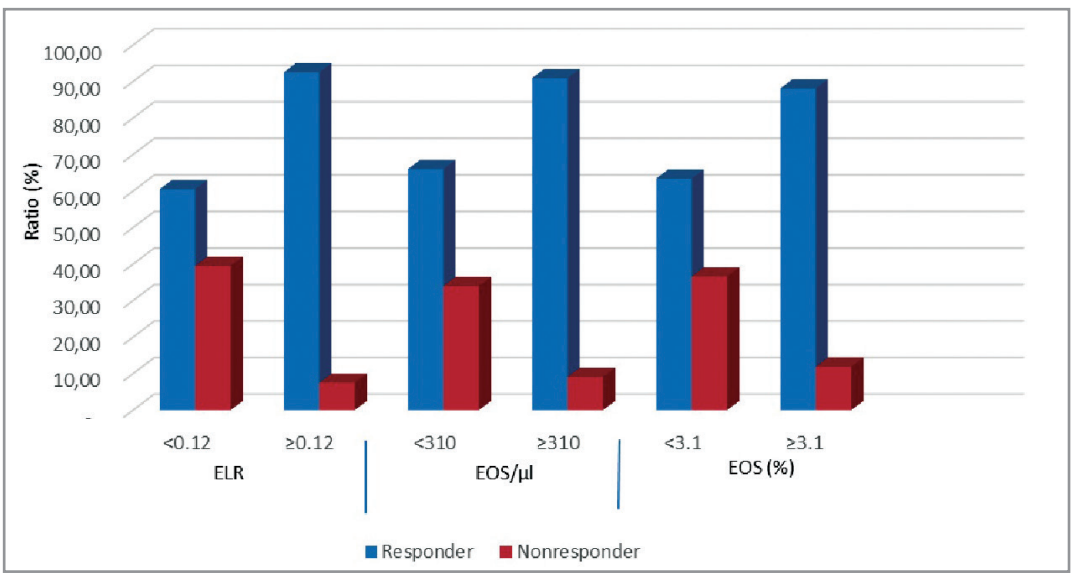

Figure 2. Relationship between the groups of responder-nonresponder and the cut off values of ELR, EOS and EOS (%).

30.366)], the rate of benefit in patients with EOS level ≥310/μL is 5 times [ODDS rate for EOS is 5.152 (95% CI: 1.372-19.346)] and we can say that the rate of benefit is approximately 4 times higher in cases with EOS% ≥3.1 [ODDS ratio for EOS (%): 4.269; 95% CI: 1.380-13.211)].

Although there was no significant relationship between Body Mass Index (BMI) and GETE scale, BMI tended to be lower in the group that responded. (27.9-32.05 kg/m^2; p= 0.06).

The incidence of side effects after omalizumab treatment was 13.0% (n= 11). These side effects were generally described as transient hypotension, hypertension, weakness, local injection site tenderness and pain, and tinnitus. Treatment was discontinued in one patient due to general body-bone pain. In one case, treatment was discontinued on a patient's own request after palpitations. These two patients were those who had not completed 1 year of treatment yet and so not included in the study.

DISCUSSION

In our study after omalizumab treatment, clinically significant improvement in ACT; a significant decrease in emergency admissions, hospitalizations and systemic steroid needs were detected. Also it was observed that the need of using montelukast and theophylline decreased significantly. When spirometric changes after treatment were examined, a significant increase was found not only in FEV_1 and % FEV_1, but also in FEF_{25-75} and % FEF_{25-75}. According to the GETE scale used to evaluate omalizumab treatment response, the rate of patients signed as responder was 75.9%, while the rate of nonresponder was %24.1. When the two groups were compared, it was found that the eosinophil level, EOS% and ELR were significantly higher in the responder group. The cut-off values according to the ROC curve were determined as 0.12 for ELR, 310/mL for eosinophil and 3.1% for % eosinophil respectively.

In our study as in many other studies, the number of attacks, hospitalizations and systemic steroid need of the patients decreased with omalizumab treatment. Based on the median values, a 100% decrease was found for all these parameters, while on average, there was a decrease of 90% in the number of emergency admissions, 85.5% in the number of hospitalizations and 81% in the annual steroid use. These rates were found to be compatible with the 15-month real life data of Bavbek et al. (95%, 86%, 83% respectively) (19). Not only systemic steroids, but also 20% reduction in theophylline use and 14.7% reduction in montelukast use were observed. Bavbek et al. generally found a 28% reduction in other drug use (19). In our study, no significant reduction was found in the use of inhaler steroids or β2 agonists.

In the study conducted by Yorgancıoğlu et al. (20), ACT increased from 9.6 to 20.4 in average after omalizumab treatment, and in our study it is increased from 8.35 to 19.23 in accordance with this study. All patients who responded to treatment were brought under control with omalizumab treatment, while initially not under control. In our study, it was determined that FEV_1 value increased from 1.69 to 1.90 lt, while FEV_1 % increased from 58.89% to 66.7%. In the study conducted by Barnes N et al. (18) they found that FEV_1 level increased from 1.99 to 2.22 lt, and % FEV_1 level increased from 62.9% to 78.6% at the end of an average of 1 year of treatment. While they detected a significant improvement in the PEF value too in their studies, in our study a significant improvement was observed in the FEF_{25-75} level and percentage rather than PEF. As noted, it was observed that the average basal FEV_1 level of our asthma patients was lower (1.69 to 1.99), and the average PEF level was higher (3.98 to 2.96). This may be due to the difference in patient groups in studies with predominantly large airway or small airway obstruction. Besides, no significant improvements were found in FEV_1 level in a randomized controlled study (21).

In Bosquet and his crew's INNOVATE based study (16), they defined the patients with a treatment response as the patients with completely controlled asthma or with a 0.5 point increase in the quality of life test. Responders were found to be 61%, less than compared to our study. However, in the PERSIST study (17) in which evaluating omalizumab treatment response was evaluated by using the GETE scale and in another study conducted by Barnes N et al. (18) , in which patients who continued treatment after 16 weeks were evaluated as the group with a responder, the rate of patients with a response was determined as 82% close to our work. They thought that the reason for this relatively high rate may be due to the high number of patients with severe asthma.

Blood eosinophils ≥260/μL, FeNO≥ 20 ppb, symptoms associated with allergen exposure and a history

of childhood onset asthma reported as predictors predicing omalizumab response in severe asthma according to the GINA guide (1). Besides in EXTRA study (22) which investigated omalizumab treatment response, it was shown that high exhaled nitric oxide (FENO) level (≥19.5 ppb), high eosinophil level (≥260/μL) and high periostin level (≥50 ng/mL) were associated with omalizumab treatment response. In another study, it was shown that omalizumab treatment reduced attacks by 59% compared to placebo in patients with eosinophil levels of 300/μL and above (23). In our study, the rate of patients with high eosinophilia (≥260/μL) was 48.2%, while the rate of those with low eosinophilia (<260 μL) was 52.8% and in our nonresponder group high eoshinophilic asthma ratio was 25%, low eoshinophilic asthma was 75%. In other words, in our study in accordance with these studies, treatment nonresponsiveness was more pronounced in the group with low eosinophil levels. However, in the STELLAIR study (24) similar efficacy was observed in patients with high (≥300/μL) and low (<300/μL) eosinophils, which was a real-life study in which omalizumab treatment response was evaluated with GETE scale, 40% reduction in attacks and both together. In the latest PROSPERO study (25), treatment response was evaluated as a 50% reduction in attacks, improvement in ACT and in FEV_1, patients with high baseline eosinophil levels were more likely to be in only ACT responders. After these studies, the EXRA study, which included a higher attack frequency in the placebo arm, was reevaluated and revealed that no differences in exacerbation frequency between high- and low-biomarker subgroups in the omalizumab arm. But in our real life study, omalizumab response was evaluated with GETE scale rather than reduction in attacks or improvement of ACT and FEV_1. It should be kept in mind that individual patients may benefit from these different parameters with omalizumab treament.

We found the cut-off point ELR as 0.12, EOS% as 3.1% and eosinophils as 310/μL in determining omalizumab treatment response according to GETE scale. While the sensitivity of ELR and EOS% was equal and higher than eoshinophil level (sensitivity: 58.73% vs 47.62%), ELRs specificity was higher than EOS% (specificity: 85% vs 75%). However, there was no significant relationship with NLR and omalizumab response. In a study conducted by Zhang et al included 164 uncontrolled asthmatic patients, the relationship between sputum and serum eosinophil rates was evaluated and it was emphasized that EOS% and ELR showed the best correlation (26). In our stud, the higher rates in sensitivity can be explained by the fact that ELR and EOS%, which are a better indicator of the eosinophilic phenotype with better omalizumab efficiency. In other words, we can say that the distribution rate of eosinophils in peripheral white blood cells gives better information about eosinophilic inflammation than the absolute value of eosinophils. In addition, in a cross-sectional study, asthmatic patients and healthy control groups were compared, not only ELR but also sections such as Eosinophil-Neutrophil Ratio (ENR) and Eosinophil-Monocyte Ratio (EMR) were higher in asthmatics than controls and were negatively correlated with ACT (27). So, there were studies showing that eosinophil rates confirm the diagnosis of asthma and reflect the level of control better. But to our current knowledge, there is no study showing the superiority of ELR in evaluating the therapeutic efficacy of omalizumab or any other biological agent.

In a study, which examined the relationship between BMI and omalizumab treatment response, 5-year omalizumab responses of 24 patients were examined and contrary to our study it was shown that high BMI was associated with ongoing treatment(28). However, both in the study conducted by Tepetam et al. (29) and in a letter written to the editor (30), it was shown that high BMI (34.09 kg/m^2, 35.16 kg/m^2, respectively) was associated with omalizumab treatment unresponsiveness. In our study there is no significant difference in terms of BMI in high eoshinophilic and low eoshinophilic group, but tended to be higher in nonresponder low eoshinophilic group.

Concordance with our study, in a real life multicenter study conducted in Turkey (20) the side effects related to omalizumab treatment were investigated and only mild-to-moderate side effects were seen in 12.7% of patients.

Conducting the study in a central specific branch hospital, enabled us to reach a higher number of patients with different phenotypes and this increased the strength of our study. The weakness of the study was that; not multicenter and it was designed retrospectively, hemogram and respiratory function test values of some patients could not be reached from file scans, so we could not include all the patients that screened and we were limited to the GETE scale

in evaluating the treatment response, the parameter such as reduction in attacks, improvement in FEV_1 and ACT could not be taken into account.

CONCLUSION

Omalizumab treatment is an effective and non-serious side effect treatment method that increases FEV_1 and FEF_{25-75}, which improves asthma control by reducing the number of attacks, emergency admissions and hospitalizations in patients with severe allergic asthma. Especially in patients with high BMI and low eosinophils and ELRs, omalizumab treatment response may be less due to the minimal Th2 pathway. In our study, in predicting the response of omalizumab treatment in severe allergic asthma, the ELR, which is one of the hemogram parameters, instead of expensive and invasive methods; it is correlated with treatment response and showed promise because it was cheaper and easily available. With prospective randomized controlled trials to be conducted, we can get more information about the ELR level.

Ethical Committee Approval: The approval for this study was obtained from Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethical Committee (Decision no: 116.2017.008, Date: 24.05.2017).

CONFLICT of INTEREST

The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: FMT, İB

Analysis/Interpretation: FMT, HÖ

Data Acqusition: FMT, İB, CÖ

Writing: FMT, HÖ, CÖ

Clinical Revision: All of authors

Final Approval: All of authors

REFERENCES

1. *Global Initiative For Asthma (GINA). Global Strategy For Asthma Management And Prevention 2020 Report. Available from: www.ginasthma.org*
2. *Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999; 160(3): 1001-8.*
3. *Simpson JL, Scott RJ, Boyle MJ, Gibson PG. Differential proteolytic enzyme activity in eosinophillic and neutrophillic asthma. Am J Respir Crit Care Med 2005; 172: 559-65.*
4. *Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-73.*
5. *Moore WC, Bleecker ER, Curan-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 2007; 119(2): 405-13.*
6. *Bulut İ. Asthma fenotypes and endotypes. Turkiye Klinikleri Arch Lung 2012; 13(Suppl 1): 28-38.*
7. *Bel EH. Clinical phenotypes of asthma. Curr Opin Pulm Med 2004; 10(1): 44-50.*
8. *Tepetam M. Astım tedavisinde yeni ilaçlar. Güncel Göğüs Hastalıkları Serisi 2015; 3(2): 173-85.*
9. *Kopp MV. Omalizumab: anti-IgE therapy in allergy. Curr Allergy Asthma Rep 2011; 11: 101-6.*
10. *Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002; 57(10): 875-9.*
11. *Haldar P, Pavord ID. Noneosinophilic asthma: a distinct clinical and pathologic phenotype. J Allergy Clin Immunol 2007; 119(5): 1043-52.*
12. *Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. Allergy 2012;67(7):835-46.*
13. *Duman D, Aksoy E, Ağca MÇ, Durmuş Kocak N, Özmen İ, Aka Aktürk Ü, et al. The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. International Journal of COPD 2015; 10: 246-78.*
14. *Louise Z, Emil Schwarz W, Simon Francis T, Vibeke B. Response to omalizumab in patients with severe allergic asthma: a real life study. Respir Med 2017; 131: 109-13.*
15. *Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosedova S, Choy DF, et al. Exploring effects of omalizumab using biomarkers. Am J Respir Crit Care Med 2013; 187(8): 804-11.*
16. *Bousquet J, Rabe K, Humbert M, Chung K F, Berger W, Fox H, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. Respir Med 2007; 101(7): 1483-1492.*
17. *Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Pilette C, et al. Real-life effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. Respir Med 2009; 103(11): 1633-1642.*
18. *Barnes N, Menzies-Gow A, Mansur Adel H, Spencer D, Percival F, Radwan A, et al. Effectiveness of omalizumab in severe allergic asthma: a retrospective UK real-world study. J Asthma 2013; 50(5): 529-36.*

19. *Bavbek S, Aydın Ö, Kepil Özdemir S, Yılmaz İ, Çelik EG, Selim Demirel Y, et al. Therapy with omalizumab in patients with severe persistent allergic asthma: a real life data in Turkey. Tuberk Toraks 2010; 58(4): 425-34.*

20. *Yorgancıoğlu A, Erkekol FÖ, Mungan D, Erdinç M, Gemicioğlu B, Özşeker ZF, et al. Long-term omalizumab treatment: a multicenter, real-life, 5-year trial. Int Arch Allergy Immunol 2018; 176(3-4): 225-33.*

21. *Costello RW, Long DA, Gaine PS, Donnell Mc T. Therapy with omalizumab for patients with severe allergic asthma improves asthma control and reduces overall healthcare costs. Ir J of Medl Sci 2011; 180(3): 637-41.*

22. *Hanania NA, Wenzel S, Rosén K, Hsieh JH, Mosesova S, Choy FD, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013; 187(8): 804-11.*

23. *Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001; 108: 184-90.*

24. *Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M; STELLAIR investigators. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J 2018; 51(5): 1702523.*

25. *Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol Pract 2019; 7(1): 156-164.e1.*

26. *Zhang X-Y, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. Clin Exp Allergy 2014; 44(9): 1137-45.*

27. *Bedolla-Barajas M, Morales-Romero J, Hernández-Colín DD, Larenas-Linnemann D, Mariscal-Castro J, Flores-Razo MM, et al. Beyond eosinophilia: inflammatory patterns in patients with asthma. J Asthma 2020; 7: 1-16.*

28. *Watanabe A, Houjyou M, Nagase H, Araj H, Kuramochi M, Ro S, et al. The relationship between baseline clinical characteristics and efficacy of omalizumab for 5 years in severe asthma. ATS Conferences. 2017.*

29. *Tepetam FM. Which ashma phenotype have poor response to omalizumab treatment? EC Microbiol 2017; 13(5): 205-209.*

30. *Gu C, Upchurch K, Davis JM, Wiest M, Lanier B, Millard M, et al. Obesity influences the outcomes of anti-IgE (omalizumab) therapy of asthma. Clin Exp Allergy 2020; 50: 1196-1199.*