ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
June 2024; 23(3):245-256.
DOI: 10.18502/ijaai.v23i3.15635

The Efficacy of Omalizumab in Patients with Chronic Rhinosinusitis with Nasal Polyps and Comorbid Severe Allergic Asthma

Emel Atayik[1], Gokhan Aytekin[1], Isa Aydin[2], and Ethem Omeroglu[3]

[1] Department of Allergy and Clinical Immunology, Konya City Hospital, University of Health Sciences, Konya, Turkey
[2] Department of ENT, University of Health Sciences, Konya City Hospital, Konya, Turkey
[3] Department of Pathology, Konya City Hospital, University of Health Sciences, Konya, Turkey

Received: 22 January 2024; Received in revised form: 28 January 2024; Accepted: 29 January 2024

ABSTRACT

Chronic rhinosinusitis whit nasal polyps (CRSwNP) is the most common comorbid disease accompanying asthma. Omalizumab is a recombinant anti-immunoglobulin (Ig) E antibody, and studies suggest that omalizumab may also affect CRSwNP regardless of asthma. We aimed to assess the effect of omalizumab treatment on CRSwNP accompanying severe allergic asthma (SAA) patients.

Clinical data including spirometry measurements, serum/nasal secretion biomarker levels were collected. NP scores and CRS scores (Lund-Mancay [LM] scores) were also recorded before omalizumab treatment, as well as at the 4th and 12th months of omalizumab treatment.

Twenty-one patients with both CRSwNP and SAA who underwent omalizumab therapy were assessed. There was a significant difference among forced expiratory volume (FEV1), ACT scores, NP scores, LM scores, serum IgE, and blood eosinophil levels of the patients before omalizumab therapy at the 4th and 12th months of omalizumab treatment. A significant negative correlation was observed between ΔFEV1 and ΔNP scores ($r=-0.485$), between ΔACT and ΔNP scores ($r=-0.469$), and ΔACT and ΔLM scores ($r=-0.436$). When we grouped the patients who benefited from 1 year of omalizumab therapy and those who did not in terms of NP, there was no difference between the two groups related to local eosinophil and local IgE levels in the nasal polyp biopsy.

Omalizumab treatment is effective for asthma and CRSwNP in patients with CRSwNP accompanied by SAA. Improvement in asthma is associated with improvement in CRSwNP. The efficacy of omalizumab on NP in patients with CRSwNP accompanied by SAA is independent of local IgE and eosinophil counts.

Keywords: Allergy; Asthma; Nasal polyps; Omalizumab; Sinusitis chronic

INTRODUCTION

Chronic sinusitis inflammation of the paranasal sinus mucosa has infectious and non-infectious causes and affects the upper respiratory tract. Nasal polyps (NPs) are benign edematous masses in the paranasal and

Corresponding Author: Emel Atayik, MD;
Department of Allergy and Clinical Immunology, Konya City Hospital, University of Health Sciences, Konya, Turkey.
Tel: (+90 332) 3105 000, Fax: (+90 332) 3105 050, E-mail emelakinci@yahoo.com

nasal cavities, or both, that can cause nasal obstruction, postnasal drip, rhinorrhea, and loss of smell.[1] Chronic rhinosinusitis with nasal polyposis (CRSwNP) is characterized by eosinophilic inflammation and an elevated concentration of immunoglobulin (Ig) E in NPs.[2,3]

Severe asthma refers to the patients having treatment for asthma in steps 4 and 5, according to the Global Initiative for Asthma (GINA) 2020 guideline, whose asthma symptoms could not be controlled with a high-dose inhaler and additional corticosteroid treatments for at least 6 months in the last year or whose asthma control is impaired when switched to a lower treatment step. Although the correct treatment and compliance with the treatment are of primary importance in asthma control, the diagnosis and treatment of comorbid diseases accompanying asthma are also very important.[4,5] NP with or without chronic rhinosinusitis is the most common comorbid disease accompanying asthma.[5,6] Approximately 5 to 15 percent of patients with severe asthma have CRSwNP, but this rate is estimated to be higher when this group of patients is evaluated radiologically and endoscopically.[7,8] Single airway disease and chronic inflammation are blamed for the association between CRSwNP and severe asthma[9]. The predominant inflammation in CRSwNP is type 2[10]. It has been shown that many of the cellular and molecular mediators, such as eosinophil cationic protein, interleukin (IL)-5, and local eosinophilic inflammation, which is responsible for the pathogenesis of asthma, also play an important role in CRSwNP.[11,12] In addition, asthma in patients with CRSwNP is related to elevated local IgE levels.[2]

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody used to treat SAA.[13,14] In some studies, it has been reported that omalizumab reduces the symptoms and severity of concomitant CRSwNP in patients with severe asthma due to similar underlying pathophysiological pathways and mediators.[7,15-17] In addition, ongoing phase studies suggest that omalizumab may also affect CRSwNP regardless of the presence of asthma.[18] Therefore, we aimed to assess the effect of omalizumab treatment on asthma symptoms and accompanying CRSwNP in severe allergic asthma patients by presenting real-life data.

MATERIALS AND METHODS

In this retrospective single-center study, the files of the patients were reviewed who were operated on for nasal polyps in the otorhinolaryngology department between January 1, 2019 and December 31, 2021, referred to the allergy and immunology outpatient clinic of a tertiary hospital due to accompanying asthma complaints, and then treated with omalizumab due to severe allergic asthma.

Demographic data of the patients, such as age, gender, body mass index, smoking status, nonsteroidal anti-inflammatory drug, and aspirin sensitivity, were recorded from patient files. Severe asthma was confirmed based on criteria set in the GINA guidelines. In addition, clinical data such as pulmonary function test results, ACT scores, blood eosinophil levels, serum IgE levels, spirometry measurements, nasal polyp scores (NPS), and CRS scores (Lund-Mancay scores) were also recorded before omalizumab treatment, at the 4th and 12th months of omalizumab treatment.

CRSwNP diagnosis was made with endoscopic and radiologic confirmation. CRSwNP was diagnosed according to the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps[1]

The patients underwent allergy testing using a skin-prick panel of 24 inhaled aeroallergens from 8 classes (dog, cat, dust mite, grass, tree, ragweed, mold, and cockroach) (ALK Abello, Madrid, Spain). A positive histamine control and a negative saline control were also included.[19]

Omalizumab treatment was adjusted according to the standard dosing schedule (total serum IgE and body weight) (Xolair; Novartis, Basel, Switzerland). Patients who achieved a decrease of at least 2 points in NPS with omalizumab treatment were considered patients who benefited from omalizumab treatment in terms of nasal polyps.[16]

Paranasal sinus computed tomography (PNSCT) CRSwNP severity scoring was performed using the Lund-Mackay CT scan score[1]. Endoscopic NPS were recorded, and the examination was performed by the ENT specialist at the beginning and end of the 12th month of treatment.

Tissue eosinophil count and local IgE from the initial nasal polyp biopsy specimens of the patients were evaluated by an expert pathologist. Four-micrometer formalin-fixed paraffin-embedded tissue sections were subjected to immunohistochemistry (IHC) using a Leica Bond-Max fully automated IHC and İn situ Hybridization (ISH) instrument (Leica Biosystems Melbourne Pty Ltd., Bond-Max, M212536, 2014, Melbourne, Australia). An IgE antibody for IHC [Rabbit

polyclonal to IgE, prediluted (ab75673); Abcam Antibodies, Cambridge, UK] and the Bond Polymer Refine Detection Kit (Leica Biosystems, Newcastle Upon Tyne, UK) were used. The exha ustive protocol was obtained from the anti-IgE product datasheet, and slides were stained with IgE (1/100 concentration) according to the protocol. All tissue sections were examined with a Nikon light microscope. The numbers of eosinophils and IgE-positive mast cells were counted in the epithelium and the adjacent lamina propria in 10 randomly selected fields (final magnification, 400×). The results were expressed as the mean number of positive cells per field.

Informed consent was obtained from the participants in the study.

IBM SPSS 20.0 (Chicago, IL, USA) statistical program was used to analyze all the data obtained during the study and recorded in the study form. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of discrete and continuous numerical variables. Descriptive statistics were presented as mean±standard deviation (SD) or median (minimum-maximum) for discrete and continuous numerical variables and as number of cases and percentages for categorical variables. Categorical variables were evaluated with the chi-square test, and continuous variables were evaluated with the t-test or Mann-Whitney U test. Analysis of nonparametric dependent variables was performed with the Friedman test, analysis of parametric dependent variables with the paired samples t-test, and analysis of categorical dependent variables with the McNemar-Bowker test. Correlation analysis between FEV1, ACT scores, blood eosinophils, serum IgE, nasal polyp scores, and Lund-Mackay scores was performed by the Spearman correlation test. The results were considered statistically significant when the p value was <0.05.

RESULTS

Twenty-one patients with both CRSwNP and severe allergic asthma who underwent omalizumab therapy were evaluated retrospectively. During the research period, no patient ended omalizumab treatment. The demographic data of the study population are summarized in Table 1.

There was a significant difference among FEV1, ACT scores, nasal polyp scores, Lund-Mackay scores, serum IgE, and blood eosinophil levels of the patients before OT and at the 4th and 12th months of OT (p<0.001, for all parameters) (Table 2 and Figure 1). After 12 months of OT, an increase of 12% (0 to 38%) in FEV1 and 7 (0 to 11) points in ACT scores were observed. In 71.4% of patients, nasal polyp scores decreased by at least 2 points, and Lund-Mackay scores decreased by at least 1 point after OT.

A significant positive correlation was observed between ΔFEV1 (Δ: represents the change between before and after 12 months of OT) and ΔACT scores after 12 months of OT (r=0.689 and p=0.001). A significant negative correlation was observed among ΔFEV1 and ΔNPS after 12 months of OT (r=−0.485, p=0.026). A significant negative correlation was observed among ΔACT and ΔNPS, as well as ΔACT and ΔLund-Mackay scores after 12 months of OT (r=−0.469, p=0.032 and r=−0.436, p=0.048, respectively) (Table 3 and Figure 2).

When we grouped the patients who benefited from one-year OT and those who did not in terms of nasal polyps, a significant difference was found among the groups in terms of disease duration, FEV1 values, and ACT scores at the 4th and 12th months of OT and nasal polyp scores before (p=0.023, p=0.009, p=0.003, p=0.011, p=0.004, and p=0.001, respectively). However, there was no difference between the 2 groups in terms of blood eosinophils, serum IgE levels, and local eosinophils and local IgE levels in nasal polyp biopsy samples before OT (Table 4). Also, there was no difference among the 2 groups in terms of ΔFEV1 and ΔACT (p=0.061 and p=0.074).

Table 1. Demographic, laboratory, and clinical parameters of the patients

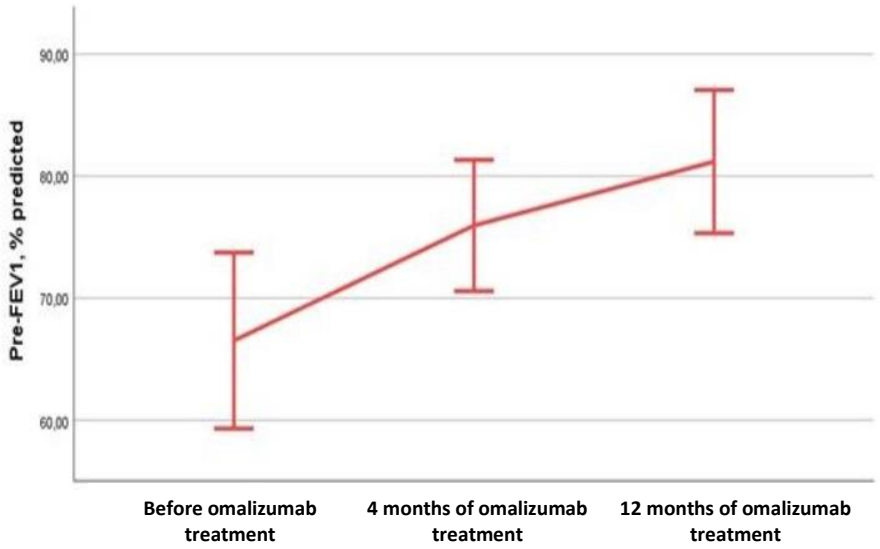
Baseline characteristics	Results (n=21)
Age, years	51 (19–62)
Gender n (%),	
Female	9 (42.9)
Male	12(57.1)
Duration of asthma, years	9 (3–30)
Non-smokers, n (%)	19 (90.5%)
Body mass index (Kg/m^2)	26 (18.8-38)
Comorbidities, n (%)	9 (42.9)
Aspirin intolerance, n (%)	13 (61.9)
ACT scores	14 (11–18)
FEV1, predicted %	67 (35–88)
Previous polyp surgery	1 (1–3)
Allergen sensitivity, n (%)	
House dust mite	10 (47.6%)
Mold	10 (47.6%)
Animal dander	1 (4.8%)
Blood total IgE level, (kU/L)	190 (32.6–3320)
Blood eosinophil count, /mm^3	1270 (277–2650)
Lund–Mackay scores	23 (14–24)
Total polyp scores	6 (4–8)
Tissue eosinophil count	83 (23–159)
Tissue local IgE	12 (3–90)

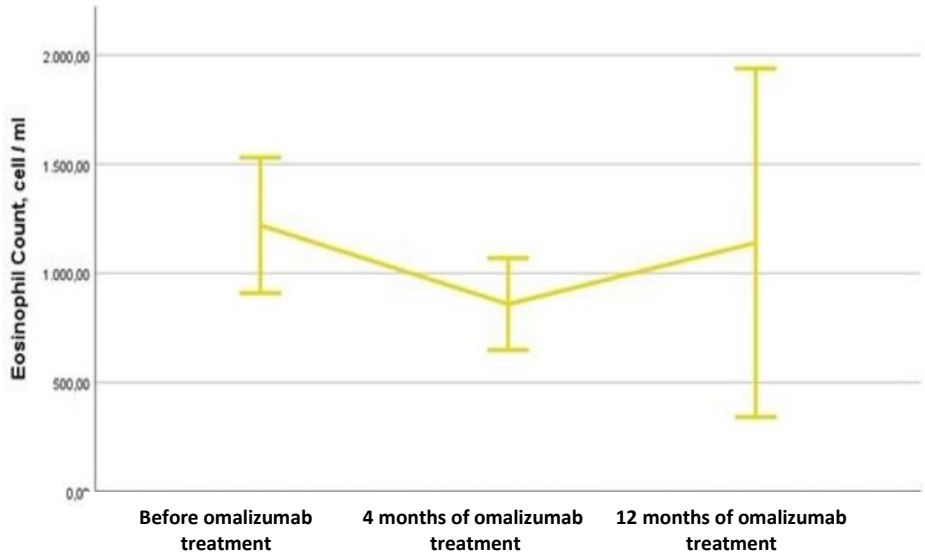
ACT: Asthma Control Test, FEV1, forced expiratory volume in 1 second, IgE: immunoglobulin E

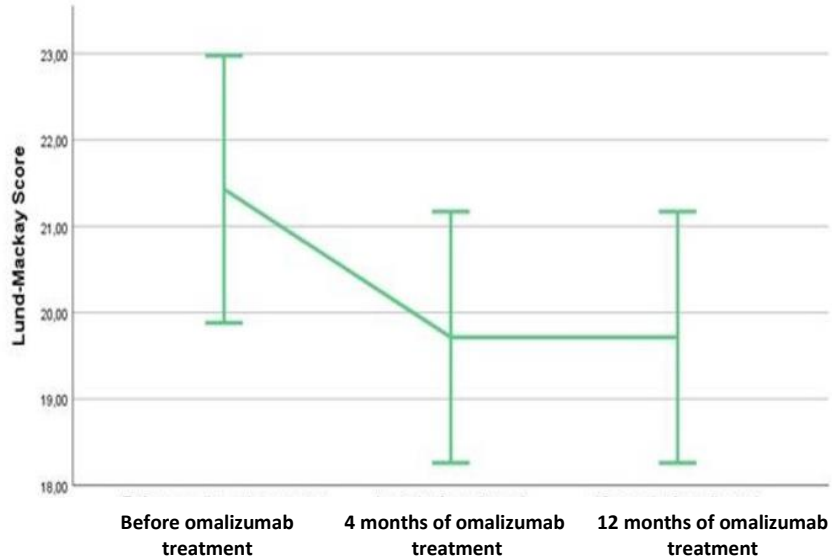
Table 2. The change of clinical and laboratory parameters during omalizumab treatment

	Before	4th month	12th month	*p*
FEV1, % predicted	67 (35–88)	72 (54–95)	84 (61–99)	< **0.001**
ACT scores	14 (11–18)	18 (13–22)	22 (13–24)	< **0.001**
Nasal polyps scores	6 (2–8)	4 (2–6)	4 (2–6)	< **0.001**
Lund–Mackay scores	23 (14–24)	21 (12–23)	18 (10–23)	< **0.001**
Eosinophil count, /mm^3	1270 (277–2650)	820 (200–1900)	820 (90–8500)	< **0.001**
Serum IgE, kU/L	190 (32.60–3320)	540 (36–5300)	643 (36–6660)	< **0.001**

ACT: Asthma Control Test, FEV1: forced expiratory volume in 1 second, IgE: immunoglobulin E.


Pre-FEV1, % predicted
90,00
80,00
70,00
60,00
Before omalizumab treatment
4 months of omalizumab treatment
12 months of omalizumab treatment


Eosinophil Count, cell / ml
2.000,00
1.500,00
1.000,00
500,00
0,00
Before omalizumab treatment
4 months of omalizumab treatment
12 months of omalizumab treatment


Lund-Mackay Score
23,00
22,00
21,00
20,00
19,00
18,00
Before omalizumab treatment
4 months of omalizumab treatment
12 months of omalizumab treatment

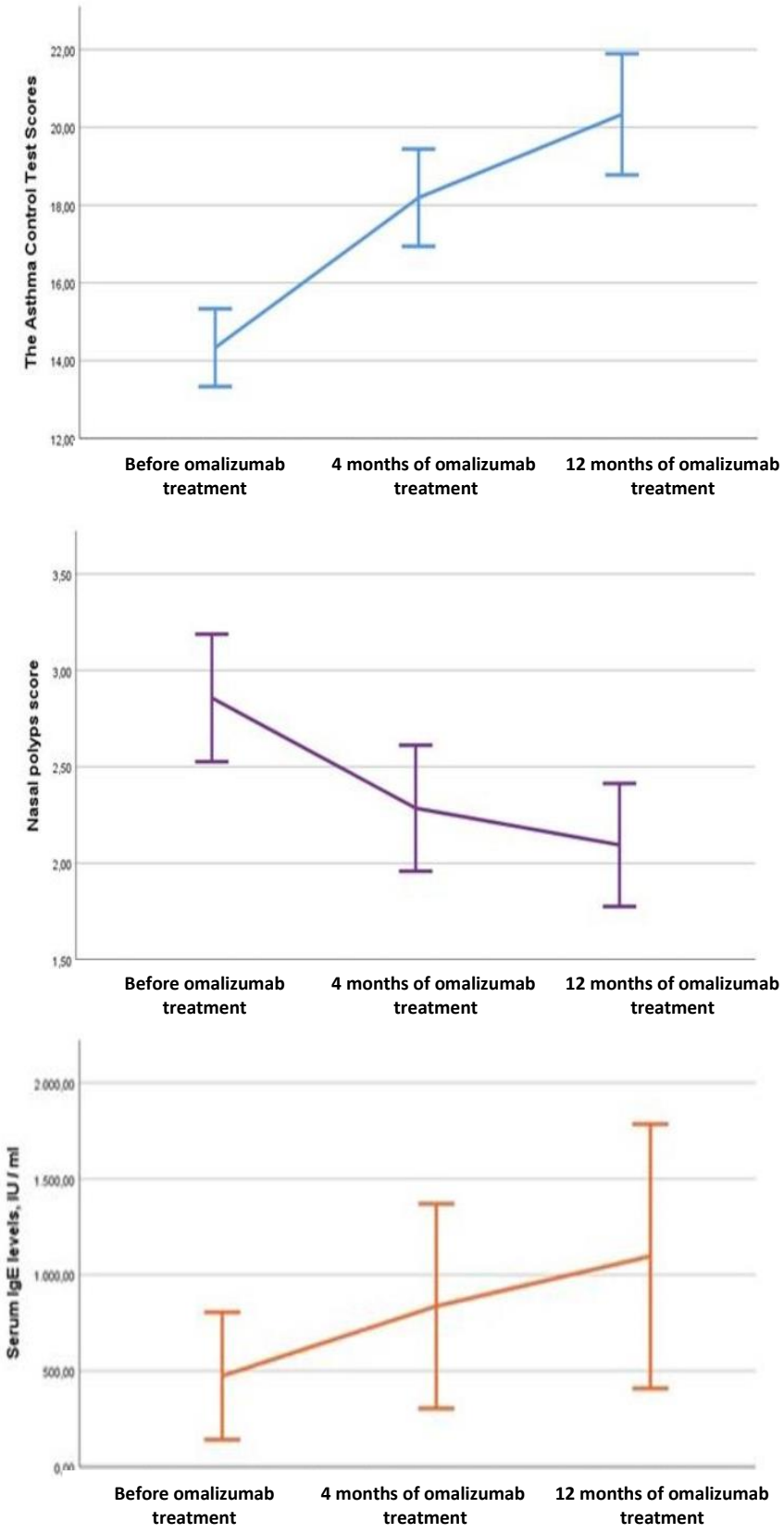


Figure 1. The change of clinical and laboratory parameters during omalizumab treatment

Table 3. The correlation of clinical and laboratory parameters with each other

	ΔFEV1		ΔACT		ΔNasal polyp score		ΔLund-Mackay score	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***
ΔNasal polyps score	–0.485	**0.026**	–0.469	0.032			0.678	0.001
ΔLund–Mackay scores	–0.245	0.053	–0.436	**0.048**	0.318	0.161		
ΔEosinophil count, /mm^3	–0.340	0.131	–0.311	0.170	0.267	0.241	–0.047	0.840
ΔSerum IgE, kU/L	0.206	0.371	0.127	0.585	–0.66	0.775	–0.059	0.799
ΔFEV1			0.689	**0.001**	–0.485	**0.026**	–0.337	0.135
ΔACT scores	0.689	**0.001**			–0.469	**0.032**	–0.436	**0.048**

Δ: the difference between before and 12th month of omalizumab therapy, ACT: Asthma Control Test, FEV1: forced expiratory volume in 1 second, IgE: immunoglobulin E

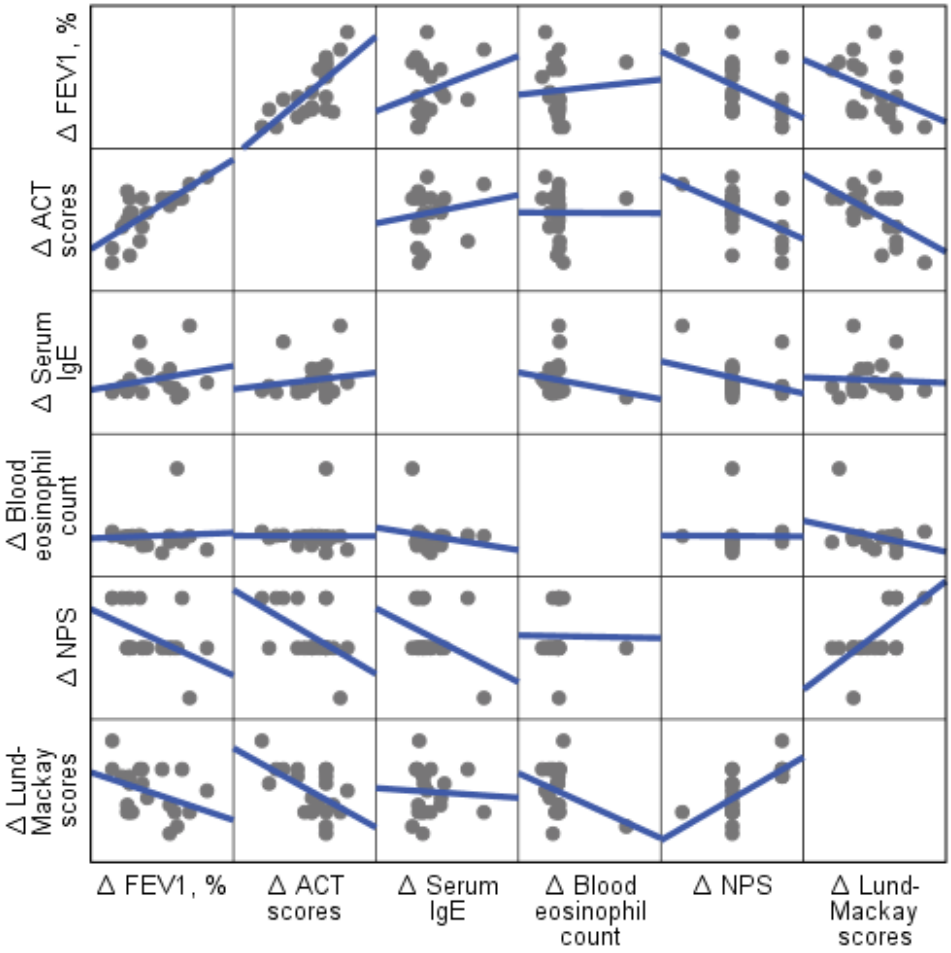


Figure 2. Correlation of clinical and laboratory parameters with each other

Table 4. Comparison of laboratory and clinical characteristics of patients with nasal polyp who benefited from omalizumab treatment and those who did not

	Patients who benefited (n=15)	Patients who did not benefit (n=6)	*p*
Age, years	43 (19–60)	53.5 (32–62)	0.138
Gender, female, n (%)	6 (40)	3 (50)	0.676
Duration of asthma, years	7 (3–20)	17 (6–30)	**0.023**
Non–smokers, n (%)	13 (86.7)	6 (100)	0.347
BMI, Kg/m^2	24.2 (18.80–35)	26 (21.60–38)	0.412
Aspirin intolerance, n (%)	8 (53.3)	5 (83.3)	0.336
ACT, before	14 (11–18)	13.5 (11–14)	0.186
ACT, 4th month	19 (14–22)	16 (13–18)	**0.009**
ACT, 12th month	22 (14–24)	16.5 (13–21)	**0.003**
FEV1, predicted %, before	68 (36–88)	65.5 (35–68)	0.160
FEV1, 4th month	82 (54–95)	68 (54–72)	**0.011**
FEV1, 12th month	90 (61–99)	67 (63–75)	**0.004**
Previous polyp surgery	1 (1–3)	2 (1–3)	0.103
Allergen sensitivity, n (%)			0.497
House dust mite	6 (40)	4 (66.7)	
Mold	8 (53.3)	2 (33.3)	
Animal dander	1 (6.7)	0	
Lund–Mackay Scores, before	24 (15–24)	20.5 (14–24)	0.088
Lund–Mackay Scores, 4th month	21 (12–22)	20 (14–23)	0.602
Lund–Mackay Scores, 12th month	18 (10–22)	20 (14–23)	0.185
Total nasal polyp scores, before	6 (4–8)	5 (2–6)	**0.001**
Total nasal polyp scores, 4th month	4 (2–6)	5 (2–6)	0.799
Total nasal polyp scores, 12th month	4 (2–6)	5 (2–6)	0.305
Blood eosinophil count, cell/mm^3, before	1380 (280–2430)	975 (277–2650)	0.533
Blood eosinophil count, cell/mm^3, 4th month	660 (270–1530)	1015 (200–1900)	0.483
Blood eosinophil count, cell/mm^3, 12th month	500 (120–8500)	1090 (90–1970)	0.243
Serum IgE, IU/mL, before	190 (32.6–3320)	243 (89.2–532)	0.938
Serum IgE, IU/mL, 4th month	540 (36–5300)	368 (75–1260)	0.484
Serum IgE, IU/mL, 12 month	685 (36–6660)	415 (75–3050)	0.484
Tissue eosinophil count	46 (23–159)	101 (75–125)	0.257
Tissue local IgE	10 (3–90)	42.5 (4–85)	0.364

ACT: Asthma Control Test, FEV1: forced expiratory volume in 1 second, IgE: immunoglobulin E

DISCUSSION

In this study, we evaluated the effect of 1-year OT on both SAA and CRSwNP, and the main results we obtained are as follows: 1) OT is effective on SAA and CRSwNP accompanying severe allergic asthma. 2) An increase in ACT scores and FEV1 (%) and a decrease in Lund-Mackay and total NPS were observed with 1-year OT. Improvement in asthma symptoms is along with improvement in CRSwNP. 3) Patients who did not benefit from OT in terms of NP had a longer duration of asthma than those who did. 4) The effectiveness of OT on nasal polyps in patients with asthma and CRSwNP is independent of local IgE and eosinophil levels obtained from biopsy samples and serum IgE and blood eosinophil levels.

In previously reported case series and studies, it has been suggested that OT in SAA patients is effective against CRSwNP as a comorbid condition. OT may be a new treatment option for CRSwNP independent of allergic asthma.[2,15,16,20,21] Gevaert et al, reported a significant decrease in total nasal polyp scores (−2.67 points) and Lund-Mackay scores (4 points) with improvement in Asthma Quality of Life Questionnaire scores compared to the placebo group in 23 patients with allergic and non-allergic asthma and concomitant CRSwNP with OT for 16 weeks.[2] In our study, after 12 months of OT, a 12 percent increase in the FEV1 value and a 7-point increase in the ACT scores of the patients were observed, as well as a decrease of at least 2 points in the TNPS's in 71.4% of the patients and at least 1 point decrease in the Lund-Mackay scores in 71.4% of the patients. Our results are consistent with the literature.

Another finding of our study was that ΔFEV1 and ΔACT were positively correlated and ΔACT was negatively correlated with ΔNPS and ΔLund-Mackay scores. In other words, improvement in asthma symptoms is accompanied by improvement in nasal polyps and chronic rhinosinusitis. The similar positive effect of OT on different diseases and the improvement in asthma accompanying the improvement in CRSwNP support the idea that common pathological pathways are responsible for the development of asthma and CRSwNP.

Many epidemiological, clinical, and pathophysiological studies have shown that asthma and CRSwNP are closely related.[16-18,22,23] There are some pathophysiological similarities between CRSwNP and asthma. Epithelial barrier dysfunction is present in both diseases and shares the same type-2 immunopathology. Upregulation of type-2 cytokines such as IL-4, IL-13, and IL-5 and release of IgE-mediated immune mediators have been demonstrated in both the lower and upper airways of asthma patients with CRSwNP.[23,24]

It is still unclear how omalizumab exerts a beneficial effect on CRSwNP. Omalizumab prevents IgE binding to its higher affinity receptors on basophils and mast cells via binding to free IgE molecules and decreases the secretion of IL-4, IL-5, and IL-13 from mononuclear cells[25]. Blood and tissue eosinophil counts decrease due to the decrease in IL-5 levels.[15] In our study, we also observed a decrease in blood eosinophil levels with omalizumab treatment.

In addition, there is an increasing number of studies showing that OT is effective on NP, independent of allergic asthma[25]. In the recent studies of POLIP-1 (n=138) and POLIP-2 (n=127), 24 weeks of OT resulted in a 0.9 to 1.1 point reduction in NPS in patients with inadequately controlled CRSwNP whose nasal polyp score was 6 or higher. It has been shown to be effective on nasal discharge, odor, and congestion symptoms independent of asthma.[18] Djukanovic et al. also showed that airway inflammation markers decreased significantly after OT.[26]

In our study, nasal polyp patients who did not benefit from OT had a longer duration of asthma than the patients who did. In addition, patients who did not benefit from OT were older than those who did, but this difference was insignificant. It has been shown that the prevalence of NP significantly increased with increasing age and duration of asthma.[22] It can be thought that prolonged asthma duration and increased inflammation in the airways may contribute to the remodeling process in the nasal mucosa, considering that the nose, including the lower airways and paranasal sinuses, is a single airway.[27] In a study reported by Wu et al., the patients with NP and comorbid asthma were separated into 3 groups (group 1: NP and atopy, group 2: NP and smoking, and group 3: NP and older). The authors stated that patients in group 1 have intermediate disease duration and less severe asthma, and patients in group 3 have longer asthma duration and a non-eosinophilic airway phenotype.[28] In our study, we can say that the patients who did not benefit from OT in terms of NP showed similar characteristics to group 3. In addition, we achieved higher FEV1 and ACT scores in patients who benefited from 4 and 12 months of OT in terms of NP than those who did not, despite having similar FEV1

and ACT scores before treatment. This condition supports our idea that non–type-2 inflammation or non–IgE-mediated inflammatory pathways may be involved in the disease process of the patients who did not benefit from OT. The exact etiology of nasal polyps is unclear; however, it is multifactorial. Only total serum IgE levels, local eosinophilic inflammation, and local tissue IgE levels are not related.[3] Other cytokine and cellular inflammatory markers may alter the omalizumab effectiveness in the treatment of NP and, consequently, the diameter of the polyp in the predominant one.

In our study, the omalizumab treatment dose was calculated according to the patient's serum IgE levels and body weight. It is also recommended that the omalizumab dose be given according to serum total IgE levels and the patient's body weight in the treatment of CRSwNP, independent of SAA.[2,15] In addition, it has been shown that local tissue IgE production has a decisive role in the pathogenesis of CRSwNP and that IgE concentration in the tissues of CRSwNP is correlated with eosinophil markers. Bachert et al. reported that CRSwNP patients with asthma are characterized by tissue eosinophilia and increased local IgE.[29,30] For this reason, it has been suggested that local eosinophilic inflammation, detection of local tissue IgE levels, and serum total IgE levels should be evaluated together in determining the dose of omalizumab in patients with severe airway diseases such as CRSwNP and asthma.[11] Since there is no definite allergen trigger for local IgE production in CRSwNP, the detected local IgEs are polyclonal and mostly against *Staphylococcus aureus* enterotoxins.[2,7,15,30] In our study, although the IgE level and eosinophil count in nasal biopsy samples were lower in NP patients who benefited from OT, this difference was insignificant. We think that the main reason for this finding is the small size of the study population. In addition, possible differences in the use of medications such as intranasal steroids and macrolide antibiotics, which may affect the cell population in the inflamed nasal tissue, may have affected local IgE and local eosinophil levels before nasal polyp biopsy. This finding suggests that the effect of omalizumab on NP is not only through IgE and eosinophil, but also that additional mechanisms may be involved, which need to be elucidated in further studies.

The main strength of our study is the inclusion of a 12-months period and the presentation of real-life data. On the other hand, the main limitation of our study is its retrospective design and limited sample size (21 patients). In addition, the absence of a control group, such as the CRSwNP patients without asthma or the placebo group, reduces the power of our results.

In conclusion, OT is effective for asthma and CRSwNP in patients with SAA accompanied by CRSwNP. In addition, improvement in asthma is associated with improvement in CRSwNP. Although the duration of asthma is longer in NP patients who do not benefit from OT, the efficacy of omalizumab on NP in patients with SAA accompanied by CRSwNP is independent of local IgE and eosinophil counts, and serum IgE and blood eosinophil levels.

STATEMENT OF ETHICS

The ethics committee approval was obtained from Karatay University Ethics Committee (with a decision dated June 19, 2020 and numbered 2020/004).

FUNDING

No funding was secured for the study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

Not applicable

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