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Efficacy of Omalizumab Treatment in Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap (ACO)

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ABSTRACT

Objective: Although the precise definition of asthma-chronic obstructive pulmonary disease overlap (ACO) is still controversial, patients sharing common features of both diseases are frequently seen in clinical practice. Current literature suggests that patients with ACO have higher risk of morbidity and mortality than those with asthma or chronic obstructive pulmonary disease (COPD) alone. Omalizumab, a monoclonal anti-IgE monoclonal antibody, has proven to be effective in moderate-to-severe allergic asthma, but data on the efficacy of omalizumab in patients with ACO are limited. To determine the efficacy of omalizumab in patients with ACO.

Materials and Methods: We assessed the effectiveness of omalizumab on 12 patients who met the criteria of ACO, using data from medical files of patients with severe allergic asthma who were treated with omalizumab between 2013 and 2018 at a University hospital.

Results: Five (41.7%) patients responded well and seven (58.3%) patients responded partially to omalizumab treatment. Decreased number of hospitalizations and exacerbations (p = 0.016 and p = 0.003, respectively) and increased asthma control test results (ACT) (p=0.003) were observed after omalizumab treatment. No significant improvement in pulmonary function tests (FEV1%, FEV1(liter), FEV1/FVC) was found (p=0.444, p=0.208, p=0.510, respectively).

Conclusion: Omalizumab was found to reduce asthma exacerbations and improve asthma control in a group of patients with ACO.

Keywords: Asthma-COPD overlap, exacerbation, hospitalization, omalizumab, pulmonary function

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases characterized by chronic airway inflammation and limited airflow. These diseases are classically regarded as distinct entities with unique genetic and environmental risk factors. However, a subset of patients with asthma or COPD present with similar clinical features and laboratory abnormalities (1). While the term ''ACO'' (asthma and COPD overlap) provides a comprehensive view of this phenomenon, it also brings new clinical challenges concerning diagnosis management (2). Indeed, several groups have attempted to define diagnostic criteria for ACO, but until recently no international consensus has been reached (3-5).

Previous studies have found that the prevalence of ACO ranges from 0.9-11.1% in the general population, 11.1-61.0% in asthma patients, and 4.2-66.0% in COPD patients depending on the diagnostic criteria used (6, 7). Despite this highly variable prevalence, given the fact that approximately one in 12 people worldwide suffer from either asthma or COPD, it is reasonable to claim that ACO is an important public health issue (8). Furthermore, recent studies have shown that patients with ACO experience faster rates of diminished lung function, more frequent symptom exacerbations, poorer quality of life, and increased mortality rates than patients with asthma or COPD alone (9-12). As a result, the current state of our knowledge pertaining to the diagnosis and treatment of ACO does not meet the needs of this patient population.

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Omalizumab (anti-IgE) has proven efficacy in the treatment of severe allergic asthma and has been used safely for many years. Some case reports declared that omalizumab is also an effective treatment option for many other allergic and non-allergic diseases such as non-atopic asthma, nasal polyps, and allergic bronchopulmonary aspergillosis (13). Furthermore, omalizumab has been studied in small case series of ACO patients, but data on the efficacy of this drug in this setting remain limited.

In addition to the high morbidity and mortality of ACO, there is no effective biological agent in its treatment. Based on this hypothesis, we aim to determine the efficacy of omalizumab in patients with ACO. As a tertiary care center located in the South Marmara region of Turkey, we have been using omalizumab for patients with severe allergic asthma since 2008. Therefore, to address the knowledge gap pertaining to the use of omalizumab in the setting of ACO, we analyzed the clinical outcomes of omalizumab treatment in ACO patients with persistent symptoms or exacerbations despite optimal treatment.

MATERIALS and METHODS

Study Design and Subjects

This retrospective clinical study was performed at the Department of Chest Diseases, Division of Clinical Immunology and Allergy, at Bursa Uludag University between January 2013 and December 2018. The study was approved by the local ethics committee of Bursa Uludag University (Approval number: 2019-4/9). Informed consent was not required for this retrospective, noninterventional analysis. Medical records data from patients with severe allergic asthma who were treated with omalizumab were used. Patients with a diagnosis of ACO based on the criteria proposed by Sin et al. were included in this study (5). Specifically, patients with ACO had to present with three of the following major criteria and at least one of the following minor criteria: major criteria- persistent airflow limitation (post-bronchodilator [FEV1/FVC]≤ 0.70) for patients ≥ 40 years of age; a smoking history of ≥ 10 -pack years or equivalent indoor or outdoor air pollution exposure; and a documented history of asthma before 40 years of age or a ≥ 400-ml increase in FEV1 following bronchodilator use; minor criteria- a documented history of atopy; a ≥ 200-ml and 12% increase in FEV1 after bronchodilator use at two or more visits; and a peripheral blood eosinophil count of ≥ 300 cells/μL.

Of the 200 patients who were treated with omalizumab for severe persistent asthma, 188 patients were excluded because they did not meet the diagnostic criteria for ACO. Thus, 12 patients who received omalizumab treatment and met the diagnostic criteria for ACO were included in this study.

Omalizumab was administered as a supplemental therapy to adult patients with severe persistent asthma who exhibited the following characteristics: 1) inadequate response to treatment with high-dose inhaled corticosteroid (ICS)/long-acting beta 2 agonist (LABA) and leukotriene receptor antagonist (LTRA) and/or long-acting muscarinic antagonist (LAMA); 2) a positive skin test or in vitro reactivity to least one perennial allergen (e.g., house dust mite, cat or dog hair, cockroaches and mold); and 3) a total serum IgE level of 30-1500 IU/ml. Personalized omalizumab treatment regimens were calculated according to each patient's body weight and total serum IgE level, and administered via subcutaneous injection every two or four weeks.

Clinical Metrics

The following patient data were collected in this study: demographic information; clinical and laboratory characteristics (e.g., smoking history, asthma/COPD disease duration, history of accompanying rhinitis/sensitivity to perennial allergens, total serum IgE level, peripheral blood eosinophil count, skin prick test [Alk-Abello, Lincoln Diagnostics, Dallas, TX, USA] and/or specific IgE results [measured using ImmunoCap, Thermo Fisher Scientific/Phadia, Uppsala, Sweden]); pulmonary function (PF) before and after omalizumab administration (post-bronchodilator FEV1, FVC, and FEV1/FVC ratio); utilization of asthma medications (use of conventional drugs and doses, onset data and application interval of omalizumab treatment); and outcomes (symptom control, asthma control test [ACT] results, and the number of asthma exacerbation episodes and hospitalizations before and after omalizumab treatment. Pulmonary function test (PFT) data and ACT scores were collected at the pre-omalizumab and the last visit of patients. Additionally, data for asthma exacerbations and hospitalizations within a 12-month period were collected for patients who received omalizumab for at least one year.

Assessment of Treatment Response

Response to omalizumab treatment was assessed according to symptom control, improvements in PF, and

decreases in the annual rates of exacerbations and hospitalizations. "Exacerbation" was defined as a worsening of asthma/COPD requiring oral corticosteroid use and/or an emergency room visit. Patients were classified as good responders, partial responders, or non-responders according to the physicians' assessments. Patients were defined as good responders if they experienced significant improvements in symptom control and/or PF, and exhibited reductions in annual exacerbation and hospitalization rates of ≥ 50%. Patients were defined as partial responders if at least one of these parameters was not achieved, whereas non-responders did not achieve any of these parameters.

Statistical Analysis

The suitability of the variables to normal distribution was examined by the Shapiro-Wilk test. Continuous variables were expressed as median (minimum: maximum) and mean ± standard deviation, and categorical variables were expressed as n (%). Dependent sample t test, Wilcoxon signed ranks test were used in the comparisons made according to normality test results. The Fisher Freeman-Halton test was used to compare categorical variables between groups. Pearson and Spearman correlation coefficients were calculated by correlation analysis between discontinuous and continuous variables. Statistical analysis was performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.), and $p < 0.05$ was considered statistically significant.

RESULTS

Twelve adult patients (8 females and 4 males) with a mean (± SD) age of 55.7 ± 6.28 years were included in the study. The mean body weight was 83.25 ± 13.23 kg. All patients were former smokers with a mean smoking history of 31.6 ± 18.02 pack-years. Mean age at asthma diagnosis was 35.5 ± 2.88 years. The mean disease duration was 20.25 ± 7.5 years. All patients had accompanying allergic rhinitis. Additionally, six patients (50%) had house dust mite sensitivity, two patients (16.7%) were sensitive to mold, one (8.3%) patient was allergic to cats, and three patients (25%) were sensitive to both home dust mites and mold. The median number of peripheral blood eosinophils was 270 (range: 50-580) cells/μL, whereas the average total serum IgE level was 87.3 (range: 30-850) IU/ml.

All patients were treated with high dose ICS/LABA and LTRA. Additionally, 10 patients were taking LAMA and eight patients were taking slow-release theophylline. Two patients were under treatment with oral corticosteroid therapy. The omalizumab treatment duration ranged from 14 to 67 months (mean: 33.25 ± 16.5 months) (Table I) and no local or systemic reactions were observed.

Table I: Demographic and clinical/laboratory characteristics of the patients.

Age, Sex	Disease Duration (yr)	Total IgE kIU/L, Eosinophil cell/μL	Omalizumab dose (mg), treatment duration (m)	FEV1(%) b/a	FEV1 (liter) b/a	ACT b/a	Exacerbations /yr b/a	Hospitalizations /yr b/a	Response
46, M	8	91.1/190	300/m, 49	16/25	0.63/0.82	7/22	5/0	1/0	Good
61, F	30	30/300	300/m, 19	49/57	1.08/1.24	6/20	1/0	0/0	Good
51, M	15	223/350	600/m, 67	70/64	2.30/2.08	12/22	6/3	0/0	Partial
47, F	10	34/50	300/m, 20	77/81	1.81/1.88	6/16	3/1	0/0	Good
54, F	25	32.2/170	300/m, 30	45/26	1.08/0.61	-/5	6/2	3/1	Partial
61, F	25	83.5/160	150/m, 22	68/77	1.41/1.56	8/18	4/4	2/1	Partial
52, M	15	32/320	300/m, 25	43/42	1.82/1.48	10/19	1/0	0/0	Partial
63, M	25	51/240	150/m, 35	68/48	1.69/1.18	5/11	20/6	3/1	Partial
64, F	30	127/170	225/2w, 45	33/36	1.76/0.81	6/18	4/2	2/0	Partial
62, F	25	850/510	525/2w, 52	55/100	1.31/1.80	5/17	24/2	6/0	Good
53, F	15	436/350	375/2w, 14	37/61	-/1.25	5/12	12/3	3/1	Good
55, F	20	488/580	525/2w, 21	87/80	2.28/1.84	6/23	6/0	0/0	Partial

F: Female, **M:** Male, **b:** Before omalizumab, **a:** After omalizumab, **yr:** Year, **m:** Month, **w:** Week, **ACT:** Asthma control test.

Following omalizumab treatment, five patients (41.7%) were classified as good responders, whereas seven patients (58.3%) were classified as partial responders. Additionally, the mean ACT score was increased to 18 (p=0.003 vs. before omalizumab treatment); this improvement was not associated with age, duration of asthma, number of peripheral blood eosinophils, or serum total IgE levels (p=0.62, 0.45, 0.23, 0.31, respectively). Furthermore, the median number of annual hospitalizations was 1.5 (range: 0-6), whereas the median number of annual asthma exacerbations was 5.5 (range: 1-24); both values were significantly decreased compared to the 12-month period prior to beginning omalizumab treatment (p=0.016 and p=0.003, respectively) (Figure 1). No statistically significant differences in PF were observed before and after omalizumab treatment (Table 2). Currently, omalizumab is still used in 8 patients but 4 patients are treated with mepolizumab.

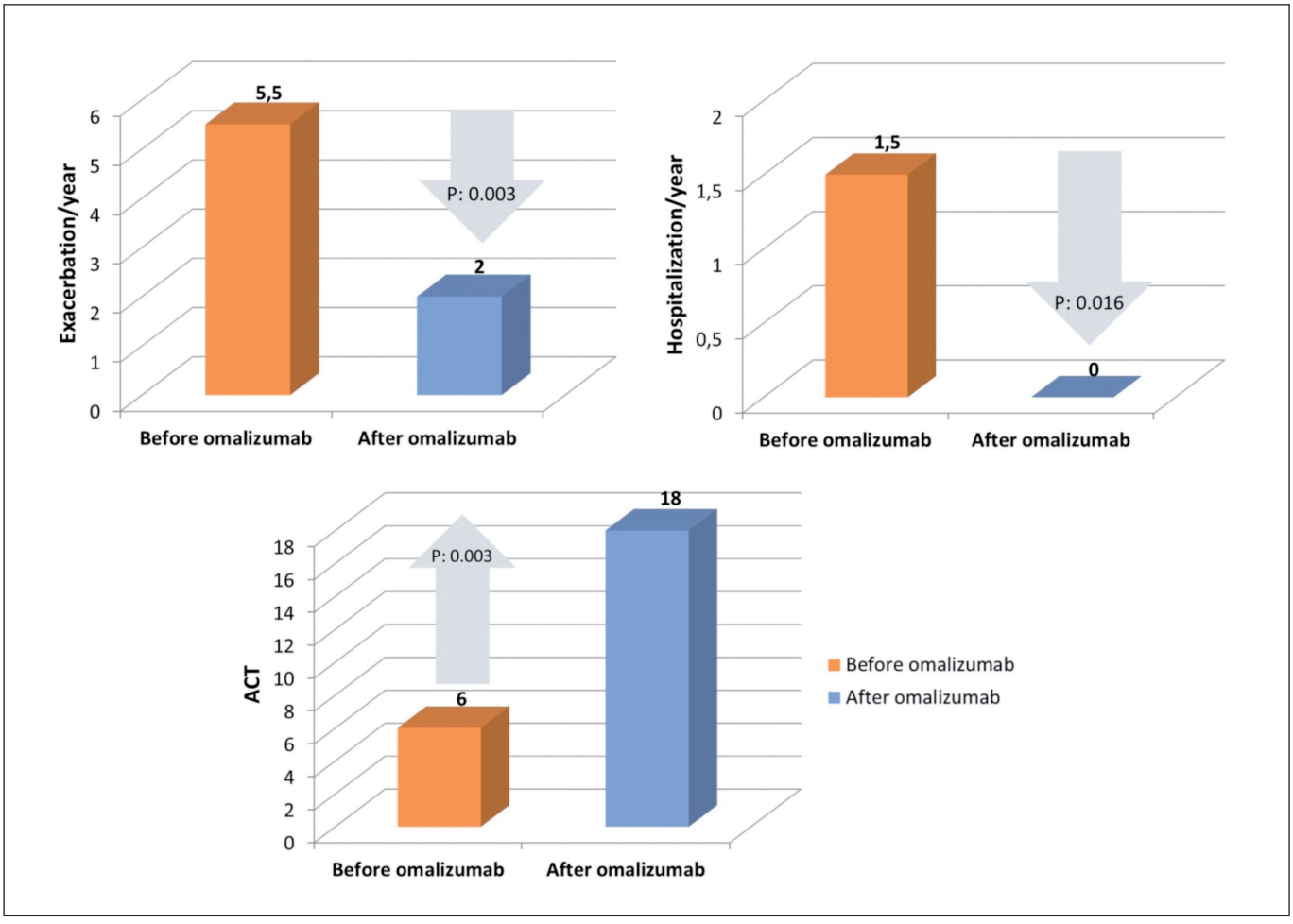

Figure 1. Clinical characteristics of the patients before and after omalizumab treatment.
ACT: *Asthma control test.*

Table II: Pulmonary function tests of the patients before and after omalizumab treatment.

	Before Omalizumab (n=12)	After Omalizumab (n=12)	*p*
FEV1/FVC (%)	58.33±8.14	60±11.42	0.510
FEV1 (%)	54±20.6	58.08±23.62	0.444
FEV1 (liter)	1.56±0.52	1.39±0.49	0.208

DISCUSSION

In recent years, ACO is a popular research area as there are lots of unknown clinic parameters both for diagnosis and treatment. Specifically, although ACO is associated with an increased risk of morbidity and mortality, there is insufficient evidence to establish strong recommendations for an optimal treatment regimen (2).

The present study demonstrated that omalizumab was effective in a subgroup with accompanying severe allergic asthma of ACO patients with respect to improving symptom control and reducing the rate of exacerbations and hospitalizations. This study adds to the current literature (mainly consisting of small case series) suggesting that omalizumab may be effective for the treatment of subgroups with accompanying severe allergic asthma of ACO. For example, Tat and Cilli's study of three cases demonstrated a reduced number of exacerbations, together with better disease control, after one year of omalizumab treatment (14). Additionally, Yalcin et al. observed statistically significant improvements in FEV1, PEF, FEV1/FVC, and ACT values within the first year of omalizumab treatment (15). Moreover, omalizumab was shown to improve asthma symptom control and patients following a six-month treatment period (16). Finally, in a post-hoc analysis of a study in which asthmatic patients undergoing omalizumab treatment were followed for 48 weeks, the clinical improvements in the ACT scores and exacerbation rates of ACO patients were similar to those of patients with asthma (17).

In contrast, omalizumab treatment did not significantly alter the PF of ACO patients in the present study. Notably, a clear link between omalizumab treatment and improvements in lung function in adult asthmatics has not been found: some studies have demonstrated improvement, while others have not (14,18-20). Interestingly, Vennera et al. reported that a two year omalizumab treatment course was associated with a statistically significant increase in FEV1 in patients under the age of 50, but not in those older than 50 years of age (20). Beyond the annual physiological decrease in FEV1, a longer disease duration, poor asthma control with frequent exacerbations, and a history of heavy smoking could result in progressive reductions in FEV1 in some of our patients. Hence, our results suggest that therapeutic responses to omalizumab in ACO patients should be evaluated based on clinical outcome measures rather than changes in PF.

Our study should be interpreted in the light of its limitations. First, due to the retrospective nature of our study, some data- ACT and PFT values in particular- were incomplete. Second, our study was limited by the low number of patients and the absence of a control group. However, it is challenging to perform studies with large case series of ACO patients, as no consensus on the definition of the disease exists. Nevertheless, given that omalizumab is not currently indicated for the treatment of patients with ACO, our study is an important step toward showing its long-term safety, as well as its clinical efficacy with respect to the symptom control and reductions in exacerbation/hospitalization rates.

CONCLUSION

Most studies treat asthma and COPD as separate entities; hence, there are considerable differences in the treatment approaches for these diseases. Recent data suggest that patients with ACO have a greater symptom burden with more frequent exacerbations and poorer quality of life than patients with asthma or COPD alone; however, there is a paucity of knowledge pertaining to ACO diagnosis and treatment. Our study revealed that omalizumab is a promising treatment option for patients with ACO with accompanying severe allergic asthma. Further prospective and controlled studies with larger sample sizes are needed to confirm and extend our findings, as a step toward recommending the routine use of omalizumab for ACO patients.

Financial/Nonfinancial Disclosures

None declared.

Conflict of Interest

Dane Ediger, Müge Erbay, Ümmühan Şeker declare that they have no conflict of interest.

Authorship Contributions

Concept: **Dane Ediger, Müge Erbay, Ümmühan Şeker,** Design: **Dane Ediger, Müge Erbay, Ümmühan Şeker,** Data collection or processing: **Müge Erbay,** Analysis or Interpretation: **Müge Erbay,** Literature search: **Müge Erbay, Ümmühan Şeker,** Writing: **Dane Ediger, Müge Erbay, Ümmühan Şeker,** Approval: **Dane Ediger, Müge Erbay, Ümmühan Şeker.**

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