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PHARMACOTHERAPY

Omalizumab treatment in asthma-COPD overlap syndromeTugba Songul Tat, MD¹ and Aykut Cilli, MD²¹Department of Internal Medicine, School of Medicine, Akdeniz University, Antalya, Turkey and ²Department of Pulmonary Medicine, School of Medicine, Akdeniz University, Antalya, Turkey**Abstract**

Introduction: Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) is a poorly understood disease with an increasing morbidity and mortality. Currently, the most effective treatment for ACOS is unknown and omalizumab for ACOS has not yet been reported. **Methods:** We report our experience with anti-IgE, omalizumab treatment on 3 patients with ACOS as a retrospective case study. **Results:** After 1 year of omalizumab treatment, patients experienced significantly lower rates of asthma exacerbation and hospitalization and better asthma control test results. **Conclusion:** Our study shows that omalizumab may be an effective and safe therapy for patients with ACOS. However larger randomized trials are needed.

Keywords

ACOS, omalizumab

History

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Introduction

In the recent document published by the science committees of both the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) was defined as a syndrome characterized by persistent airflow limitation with several features associated with asthma and COPD [1,2]. ACOS represents a distinct clinical phenotype with more frequent exacerbations and hospitalization, reduced health-related quality of life, and higher healthcare costs than either disease individually [3].

Patients with ACOS have been systematically excluded from both COPD and asthma trials; therefore there is little information about the response of these patients to most of the current pharmacological therapies. At present, GINA-GOLD documents recommend that the initial treatment of ACOS defaults towards treating for severe asthma on safety grounds specifically, avoiding the prescription of monotherapy with a long-acting bronchodilator, which, although acceptable in COPD, is associated with a substantial risk of severe life-threatening exacerbations in asthma [1,2].

The anti-immunoglobulin E (anti-IgE) treatment omalizumab is a recombinant humanized monoclonal antibody used for patients with uncontrolled moderate or severe allergic asthma. It is both effective and safe [4].

Here, we report our experience with omalizumab in three patients with ACOS who had increased IgE levels and who were sensitive to at least one perennial allergen.

Methods

Between August 2014 and September 2015, a total of 3,256 patients with asthma were evaluated in our outpatient clinic. Fifty-nine of them were treated with omalizumab, those patients having severe persistent allergic asthma sensitive to at least one perennial allergen: three of these patients had ACOS, diagnosed according to the recent guidelines of GINA and GOLD [1,2].

All patients with ACOS were ex-smokers and had persistent airflow limitation and respiratory symptoms which were becoming increasingly worse but variable over time. Chest x-rays showed hyperinflation in all three patients. CT (computed tomography) of the thorax showed emphysema in cases 2 and 3. All of the 3 patients had post-bronchodilator FEV₁/FVC ratio < 0.7 and FEV₁ < 80% predicted. Their initial diagnoses were COPD for the first two patients and asthma for the third. Duration of diagnoses were 12, 11 and 10 years, respectively.

Before omalizumab treatment commenced, all patients were on high doses of inhaled corticosteroid (ICS), long-acting beta-adrenoreceptor agonists (LABA), leukotriene receptor antagonist (LTRA) and long-acting muscarinic antagonist (LAMA). Despite this combined therapy, levels of asthma symptoms in the patients were uncontrolled. Therefore, we started omalizumab therapy. Dosages for omalizumab treatment were based on a patient's baseline total IgE and weight. Duration of omalizumab treatment in the different cases were 13, 21 and 58 months, respectively. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

Results

Patients were evaluated monthly for treatment tolerance and efficacy. Treatment efficacy was evaluated by the Asthma Control Test (ACT) [5], the number of conventional or intensive

Table 1. Baseline demographic and clinical characteristics of the patients.

	Case 1	Case 2	Case 3
Age (y), Sex	66, M	69, M	36, M
Duration of symptoms (y)	14	24	11
Symptoms	Dyspnea, cough, wheezing	Dyspnea, cough	Dyspnea, cough, wheezing
Smoking	40 pack-years	56 pack-years	15 pack-years
Allergic rhinitis	+	+	+
Symptoms worsen over time	+	+	+
Physical examination	Prolonged expiration, decreased breath sounds, rhonchi	Prolonged expiration, decreased breath sounds	Prolonged expiration, decreased breath sounds, wheezing
BMI (kg/m ²)	21.5	26	21
FEV ₁ /FVC (%)	44	62	65
FEV ₁ (lt) (%)	1.01 (34)	1.52 (54)	2.46 (62)
Radiological findings			
Chest radiography	Hyperinflation	Hyperinflation	Hyperinflation
Computed tomography	NA	Emphysema, geographic pattern	Emphysema, bronchial wall thickness
Total IgE level (IU/mL)	204	136	333
Blood eosinophil count (μl)	120	330	700
Skin Test Positivity	Dust Mites, animal dander	Dust Mites, cockroaches, grass pollen	Dust Mites, cockroaches
Asthma Control Test (ACT)	6	7	5
Level of asthma symptom control	Uncontrolled	Uncontrolled	Uncontrolled
Treatments	LABA+ICS (high dose)+LTRA+LAMA	LABA+ICS (high dose)+LTRA+LAMA	LABA+ICS (high dose)+LTRA+LAMA

BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; ICS, inhaled corticosteroid; LABA, long-acting beta-adrenoreceptor agonists; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NA, not available.

care unit hospitalizations related to asthma exacerbation and the number of exacerbations (defined as an increase in symptoms for more than 48 hours requiring a change in treatment of asthma). Spirometry was performed at inclusion and then every 3 months. Clinical characteristics and pulmonary functions of the patients before and after 1 year of omalizumab treatment are shown in Table 2.

Table 2. Pulmonary function tests and clinical characteristics of the patients before and after one year of omalizumab treatment.

	Pretreatment	Posttreatment
FEV ₁ /FVC (%)		
Case 1	44	41
Case 2	62	62
Case 3	65	64
FEV ₁ (l,%)		
Case 1	1.01 (34)	0.96 (33)
Case 2	1.52 (54)	1.15 (42)
Case 3	2.46 (62)	2.52 (64)
Asthma Control Test (ACT)		
Case 1	6	23
Case 2	7	20
Case 3	5	23
Level of asthma symptom control		
Case 1	Uncontrolled	Partly controlled
Case 2	Uncontrolled	Partly controlled
Case 3	Uncontrolled	Partly controlled
Hospitalization for asthma in the past year		
Case 1	3	1
Case 2	0	0
Case 3	3	0
Asthma exacerbations in the past year		
Case 1	6	1
Case 2	2	0
Case 3	6	1

After 1 year of omalizumab treatment, patients experienced significantly lower rates of asthma exacerbation and hospitalization and better asthma control tests. Their asthma symptom control levels became significantly better than before. However there was no improvement in pulmonary function tests. We observed no side effects, omalizumab was well-tolerated.

Discussion

The most effective treatment for patients with ACOS is unknown. At present, both a long-acting bronchodilator and an inhaled corticosteroid are recommended on suspicion of ACOS. ACOS has several phenotypes that might necessitate different therapeutic approaches. One specific treatment, as we have shown in our study, is the anti-IgE treatment of patients with raised serum IgE. To our knowledge, this is the first study that evaluates the effects of omalizumab in patients with ACOS. Our study provides evidence that omalizumab is an effective and safe therapy for patients with ACOS.

We report our experience with omalizumab in three patients with ACOS who were sensitized to at least one perennial allergen. All patients with ACOS were ex-smokers and had persistent airflow limitation and respiratory symptoms worsening over time, but variability could be seen. The ages of the patients were 66, 69 and 36, respectively. The third patient is younger and seems unlikely to have COPD, but his thorax CT revealed emphysema and bronchial wall thickness. His DLCO (diffusing capacity of the lungs for carbon monoxide) was 75% and alpha-1-antitrypsin level was normal. All of the ACOS diagnoses of patients were appropriate to the document of science committees of both GINA and GOLD [1,2].

ACT and level of asthma symptom control improved by clinically significant amounts. It is also noteworthy that the level of asthma symptom control moved out of the uncontrolled range. From the patient's perspective, this is clearly important. Lung

function was not significantly improved during the treatment period. Our study showed ACOS patients should be evaluated with alternative outcome measures instead of changes in FEV₁ in response to treatment.

Persistent airflow limitation might be the underlying mechanism for the unchanged results in pulmonary function tests. The effects of omalizumab on lung function vary in the literature. A randomized clinical trial showed significant improvements in predicted FEV₁ (71% vs 60%; $p < 0.001$) [6]. On the other hand, other studies have failed to show significant changes in pulmonary functions (FEV₁) [7–9]. In a randomized clinical trial that included children, adolescents, and young adults with persistent asthma, there were no changes in pulmonary function [9].

To the best of our knowledge, there is only one study that specifically addressed patients with ACOS. Ishiura et al. showed that a 4-week treatment with once-daily fluticasone furoate/vilanterole 200/25 mg improved lung function at least as much as was observed with twice-daily fluticasone propionate/salmeterol 500/50 mg in patients with ACOS [10].

Conclusion

This is the first study that shows the benefit of omalizumab in patients with ACOS. Our study showed that omalizumab has potential as a regular treatment for ACOS. However, it is clear that further study is needed before definitive conclusions can be made. Because ACOS is a heterogeneous disease, comprehensive therapeutic interventions for patients with ACOS need to be established.

Declaration of interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the article.

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