Marmara Medical Journal 2016; 29 (Special issue 2): 3-9
DOI: 10.5472/MMJsi.2902.02

REVIEW ARTICLE

Asthma COPD overlap syndrome (ACOS)

Derya KOCAKAYA

ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are the two most prevalent obstructive diseases of the lung. Although asthma and COPD differ in many ways some properties of each disease co-exist in some patients, particularly in patients with advanced age which recently brought up the term; Asthma-COPD Overlap Syndrome (ACOS). In addition to the fact that clinical trials deliberately exclude the patients in this group, the diagnostic criteria of ACOS are not well established. Both of these factors contribute to paucity of evidence based clinical information about ACOS. In this article my aim is to provide brief information about the history, description, clinical properties and treatment of this disease.

Keywords: ACOS, COPD, Asthma, Guideline

Introduction

Asthma and COPD are two highly prevalent forms of obstructive lung diseases, which lead to significant utilization of the healthcare systems worldwide. The hypothesis which proposes asthma and COPD to use common pathogenic mechanisms is referred as the ‘’Dutch Hypothesis’’ and was first introduced in 1960 by N. G. M Orie and H. J. Sluiter in a multidisciplinary symposium in Groningen where scientists noted that clinical expressions of the disease are determined by endogenous (i.e. genetic factors, age, sex) and exogenous (i.e. environmental such as allergens, smoking, viruses) factors. In the following years opinions for and against this hypothesis were expressed and a ‘’British Theory’’ was formed which states asthma and COPD are two distinct entities with different pathogenesis [1].

Derya Kocakaya
Department of Pulmonary and Critical Care Medicine, School of Medicine, Marmara University, Istanbul, Turkey
e-mail: drderyagun@gmail.com

The guidelines that direct our clinical practice have been highlighting the importance of correctly identifying these two diseases in order to treat and manage properly.

Definition and diagnosis of ACOS

Of these two diseases which are characterized by chronic airway inflammation, asthma is known to have a usually reversible inflammatory process which is dominated by Th2 cytokines, CD4+ lymphocytes or eosinophils and typically responds well to inhaled corticosteroids (ICS). Symptoms and signs are intermittent and may sometimes remit completely. However, in COPD inflammation is mainly mediated by Th1 cytokines with abundant CD8+ lymphocytes or neutrophils, signs and symptoms related to airway obstruction are progressive. In our daily practice we frequently observe patients with signs and symptoms of each disease which brought up the term ‘ACOS’ first time in 2007 in the Canadian Thoracic Society COPD guideline where it was recommended to treat COPD patients with prominent asthma component differently by adding ICS earlier in the course of treatment [2]. During recent years attention devoted to ACOS increased substantially and descriptions regarding ACOS were introduced both from asthma and COPD perspectives. ACOS diagnostic criteria (Table I) defined by Spanish experts in 2012 was later on incorporated into their consensus statement on ACOS and COPD Spanish guideline (GesEPOC) [3, 4]. Meanwhile some other European countries’ guidelines mentioned similar ACOS criteria as well [5]. Many of these included variables, which are neither used in daily practice nor available in many centers and mainly based on expert opinions. Many epidemiologic studies suggested the main feature of ACOS should be diagnosis of asthma before the age of 40 in a patient with COPD however this suggestion did not gain traction thus not widely accepted [6].

Table I. ACOS criteria proposed by Spanish Thoracic Society

Major	Minor
1.Very positive bronchodilator test (increase in FEV1% ≥15% and ≥400ml over baseline)	1.High total IgE
2.Eosinophilia in sputum	2.Personal history of atopy
3.Personal history of asthma (before the age of 40)	3.Positive bronchodilator test (increase in FEV1% ≥12% and ≥200ml over baseline) on 2 or more occasions

Two major criteria, or 1 major and 2 minor criteria are necessary for diagnosis.

In 2014 Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Diseases (GOLD) scientific committees issued a joint statement describing ACOS as a syndrome characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. This overlap makes differentiation of asthma and COPD difficult particularly in smokers with advanced age who have persistent airway obstruction. In order to serve this purpose essential properties of the diseases are listed followed by a separate table which identifies how many of those are possessed by the patient and which diagnosis is more favorable over the other (Tables II and III). It is suggested to consider either asthma or COPD if three or more of the disease properties listed in Table III are present or to consider the diagnosis of ACOS if patients possess similar numbers of properties of asthma or COPD [7, 8].

Furthermore, besides patients' history, physical examination and imaging studies findings it is suggested to use pulmonary function testing parameters to support the diagnosis. Pulmonary function testing parameters in asthma, COPD and ACOS are listed in Table IV [7, 8].

In the light of the aforementioned knowledge ACOS is practically defined as COPD patients with high reversibility and/or asthma patients with advanced age who do not exhibit completely reversible airway obstruction [9].

Table II. Usual features of asthma, COPD and ACOS

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood onset but can commence at any age	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV1 may be improved by therapy, but post-BD FEV1/FVC < 0.7 persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high
Chest X-ray	Usually normal	Severe hyperinflation &other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Airway inflammation	Eosinophils and/or neutrophils	Neutrophils ± eosinophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.

BD=bronchodilator, AHR=airway hyperresponsiveness

Table III. Features which favor asthma or COPD if present

Feature	More likely to be asthma if several of *	More likely to be COPD if several of *
Age of onset	• Onset before age 20 years	• Onset after age 40 years
Pattern of respiratory symptoms	• Variation in symptoms over minutes, hours or days • Symptoms worse during the night or early morning • Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	• Persistence of symptoms despite treatment • Good and bad days but always daily symptoms and exertional dyspnea • Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
Lung function	• Record of variable airflow limitation (spirometry, peakflow)	• Record of persistent airflow limitation (post-BD • FEV1/FVC < 0.7)
Lung function between symptoms	• Lung function normal between symptoms	• Lung function abnormal between symptoms
Past history or family history	• Previous doctor diagnosis of asthma • Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	• Previous doctor diagnosis of COPD, chronic bronchitis or emphysema • Heavy exposure to a risk factor: tobacco smoke, biomass fuels
Time course	• No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year • May improve spontaneously or have an immediate response to BD or to ICS over weeks	• Symptoms slowly worsening over time (progressive course over years) • Rapid-acting BD treatment provides only limited relief
Chest X-ray	• Normal	• Severe hyperinflation

BD=bronchodilator, ICS=inhaled corticosteroids

Table IV. Spirometric measures in asthma, COPD and ACOS

Spirometric variable	Asthma	COPD	ACOS
Normal FEV1 /FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV1 /FVC <0.7	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis (GOLD)	Usually present
FEV1 ≥80% predicted	Compatible with diagnosis (good asthma control or interval between symptoms)	Compatible with GOLD classification of mild airflow limitation (categories A or B) if post-BD FEV1 /FVC <0.7	Compatible with diagnosis of mild ACOS
FEV1 <80% predicted	Compatible with diagnosis Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and COPD exacerbations)	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and exacerbations)
Post-BD increase in FEV1 ≥12% and 200 ml from baseline (reversible airflow limitation)	Usual at some time in course of asthma, but may not be present when well-controlled or on controllers	Common and more likely when FEV1 is low	Common and more likely when FEV1 is low
Post-BD increase in FEV1>12% and 400ml from baseline (marked reversibility)	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

Epidemiology

Based on the diagnostic criteria of many published studies ACOS prevalence varies from 5 to 55%. Marco *et al.* from Italy reported ACOS prevalence as 1.6% in 20-44 year olds, 2.1% in 45-64 year olds and 4.5% in 65-84 year olds [10].

Investigations, which focus on databases of COPD studies and quantify the COPD patients who have documented doctor diagnosed asthma reached a quite high ACOS prevalence. Hardin *et al*. in their COPDGene study reported a prevalence of 13%. In their EPI-SCAN study Miravitlles *et al.* similarly reported that 17.4% of COPD patients have prior physician documented diagnosis of asthma [6]. A study from Barcelona, Spain reported prevalence of ACOS as 15.9% [5]. Another study by Soriano *et al*. noted that ACOS prevalence increases with age. It is 10% under 50 years olds however over 50% in patients who are over 50 years old [11]. Menezes and Hardin reported higher mean age in ACOS patients [12, 13]. Increase of prevalence with aging is thought to be related to the development of persistent airway obstruction due to inadequate treatment or ongoing insults such as smoking [14, 15]. A study by Kiljander *et al.* revealed ACOS prevalence as 27.4% in asthma patients who have a history of smoking. Smoking 20 pack years and age over 60 years were best predictors of ACOS in the study population and these risk factors together increase ACOS risk 6 fold (*p: 0.001*) [16]. The reason suggested to explain high ACOS prevalence is that asthma and airway hyper-responsiveness to be among the COPD risk factors. Lange *et al.* identified that deterioration of pulmonary functions is more rapid in asthma patients with even more prominence in smokers [17]. Another study revealed that 16% of asthma patients developed irreversible airway obstruction over a follow up period of 26 years [15].

Clinical properties

Although studies on ACOS are increasing in number, information regarding clinical properties of the disease is limited.

Brzostek and Kokot's study from Poland reported 68% of patients complained of dyspnea on exertion, 63% had wheezing and paroxysmal nocturnal dyspnea and 72% had chronic productive cough [18].

EPI-SCAN study of Miravitlles *et al*. revealed that when compared to COPD patients, ACOS patients had more dyspnea (*p<0.001*) and wheezing (92.5% vs 58.2%, *p<0.001*) but there were no differences between these two groups in terms of cough and sputum production. 6-minute walking test results between two groups were not different either [6].

On the contrary, Menezes *et al.* described ACOS patients as the patient group who complained of cough and sputum production most frequently (*p<0.001*). This study revealed dyspnea symptom is more frequent in asthma patients whereas in terms of wheezing, asthma and ACOS patients have similar frequency, which is significantly more than COPD patients [12].

de Marco *et al.* reported that when compared to COPD patients, ACOS patients had higher modified Medical Research Council (mMRC) scores, had more dyspnea, cough, sputum production and wheezing. Furthermore, ACOS patients had more frequent symptoms, more prominent physical impairment and higher number of hospital admissions [10]. Another population based cohort study of de Marco with a different group of investigators revealed when compared to asthma and COPD patients ACOS patients had worse basal pulmonary functions and their decline in FEV1 and FVC was similar to asthma patients but less than COPD patients. Additionally, respiratory problems necessitating emergency or hospital admissions were found to be twice as often in ACOS patients than COPD and asthma patients [19]. Two studies, which investigated pulmonary function parameters, revealed worse results in ACOS patients [6, 12] whereas Kauppi *et al*. and Fabbri *et al.* reported better parameters in ACOS patients [20, 21]. However, it should be noted that in none of these studies these differences reached statistical significance.

In terms of exacerbation history studies by Hardin *et al*., Miravitlles *et al*. and Menezes *et al*. revealed that when compared to COPD patients ACOS patients have more frequent exacerbations [6, 12, 13].

Serious exacerbations necessitating inpatient care are found to be more frequent in ACOS patients when compared to patients with COPD [10, 12, 13].

A study performed in South Korea revealed more significant airway obstruction (i.e. low FEV1/FVC and low FEV1% predicted), more frequent hospital admissions due to respiratory problems and higher mortality rates [22].

On the contrary, there are conflicting reports as well. A study from Australia concluded that when compared to ACOS patients COPD patients have worse prognosis, worse physical performances and more prominent decline in pulmonary

functions. Additionally, COPD patients had higher rates of mortality than asthma and ACOS patients [23].

Another report from Japan stated COPD patients had higher rates of mortality when compared to asthma and ACOS patients. Also, length of hospital stay, intensive care unit stay and duration of mechanical ventilation were longer in COPD patients [24].

CHAIN study, which was performed in Spain on a cohort of COPD patients, ACOS patients were found to have better 1-year survival rates with no significant difference in terms of exacerbation frequency [25].

Inflammation and Biomarkers

Data regarding ACOS patients and systemic inflammation are pretty limited. Available knowledge is widely extrapolated from previous asthma and COPD studies. In contrast to the eosinophilic inflammation, which is commonly observed in asthma patients, a non-eosinophilic asthma group is identified with predominant neutrophilic inflammation whose steroid response is poor. Meanwhile it is revealed that asthma patients who had persistent airway obstruction mainly suffered from neutrophilic inflammation [26].

Similarly, in COPD patients who are mainly affected by neutrophilic inflammation some patients have higher numbers of eosinophils in serum and sputum samples. These patients respond well to ICS, particularly who have high numbers of eosinophils in induced sputum [27].

According to the data we can reach to the conclusion that inflammation in asthma and COPD have different properties and some patients carry similarities to each of the groups which support the diagnosis of ACOS [28].

In 2014 Chinese investigators studied systemic inflammation in ACOS patients and checked their C-reactive protein (CRP) and interleukin-6 (IL-6) levels to compare with the available data from COPD and asthma patients, which are readily available. Study revealed that CRP and IL-6 levels in ACOS patients were higher than asthma patients and similar to COPD patients suggesting that ongoing systemic inflammation in ACOS patients is as worse as COPD patients [29].

Treatment

Studies regarding obstructive lung diseases generally exclude asthma patients when investigating COPD treatment options and the opposite is true as well. Therefore, our knowledge on ACOS treatment generally relies on treatment strategies mentioned in asthma and COPD guidelines. Treatment trials performed solely on ACOS patients are pretty limited. The aims of ACOS treatment are controlling the symptoms and decreasing the impairment while eliminating the risks of pulmonary function deterioration, exacerbations and side effects of medications. While main reasons of morbidity in ACOS are cough, sputum production, wheezing, dyspnea on exertion, physical deconditioning and medication side effects, mortality is primarily related to exacerbations resulting in respiratory failure. Main principles of treatment are achieving symptom control cost-effectively, decreasing the number of exacerbations without any major side effects, improving quantifiable functional parameters and improving quality of life [30].

Canadian Thoracic Society guideline published in 2007 contains information regarding ACOS patients and recommends long acting beta agonists (LABA) and long acting muscarinic receptor antagonists (LAMA) as primary choice of treatment while considering ICS treatment earlier in the course of patients with prominent asthma component. Meanwhile it is recommended to set different goals of treatment when compared to asthma and COPD patients with particular emphasis on patient education and self management plans [2].

Czech Pneumological and Phthisiological Society's COPD guideline recommends ICS + LABA combination as first line of treatment with proven efficacy while recommending ICS + LABA + LAMA combination as an alternative. Lastly, adjunct anti-leucotriene treatments are recommended as complementary [31].

A consensus statement from Spain in 2012 recommends ICS early in the course of treatment of every patient to suppress inflammation and using symptoms, pulmonary functions and/or sputum eosinophilia for titrating the dose of ICS. Due to the natural properties of COPD, it is recommended to add long acting bronchodilators to ICS and even consider triple therapy of ICS, LABA and LAMA if symptom control is not achieved. Even though there are conflicting statements in the consensus, early discontinuation of ICS is not recommended since this may trigger exacerbations [3].

Spanish COPD guideline published later in 2014 includes a section dedicated to ACOS patients' management where addition of theophylline to treatment in advanced cases and a phosphodiesterase inhibitor roflumilast in patients with

chronic bronchitis phenotype is recommended [4].

GINA and GOLD guidelines include joint recommendations on ACOS treatment which include ICS + LABA or ICS + LAMA or ICS + LABA + LAMA combinations. Additionally, they explicitly express which patients should be referred to experienced centers or drug trials. Patients who have persistent symptoms despite treatment, who have exacerbations, whose diagnosis is uncertain, who have additional symptoms such as hemoptysis, weight loss, night sweats, fever and bronchiectasis signs, who have comorbidities should be referred to more experienced centers. Meanwhile all patients should receive treatment and recommendations about their modifiable risk factors including smoking cessation, management of comorbidities, non-pharmacological treatments such as physical activities, pulmonary rehabilitation and vaccination and proper self management strategies and regular follow-up [7, 8].

Two case series comprising of 10 and 3 ACOS patients reported good response to omalizumab treatment while mentioning the necessity of further studies [32, 33].

Conclusion

ACOS should be kept in mind in patients who have prior diagnosis of asthma or COPD while possessing properties of each disease. To establish internationally accepted diagnostic criteria and determine treatment strategies, more studies including this specific group of patients are necessary. Our current knowledge relies on applying the proper treatment recommended by asthma and COPD guidelines according to the clinical properties of patients. If there is doubt about diagnosis or treatment, patients should be referred to experienced centers.

References

1. Postma DS, Weiss ST, van den Berge M, Karstjens HA, Koppelman GH. Revisiting the Dutch hypothesis. J Allergy Clin Immunol 2015; 136:521-9.
2. O'Donnell D E, Aaron S, Bourbeau J, et al., Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J 2007;14: (Suppl B):5B-32B.
3. Soler-Cataluna J J, Cosio B, Izquierdo J L, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol 2012; 48: 331-7.
4. Miravitlles M, Soler-Cataluna J J, Calle M, et al. Spanish COPD Guidelines *(*GesEPOC*):* pharmacological treatment of stable COPD. Spanish Society of Pulmonology and Thoracic Surgery. Arch Bronconeumol 2012;48: 247-57.
5. Barrecheguren MM, Roman-Rodriguez M, Miravitlles M. Is a previous diagnosis of asthma a reliable criterion for asthma-COPD overlap syndrome in a patient with COPD*?* Int J Chron Obstruct Pulmon Dis 2015;10: 1745-52.
6. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. Respir Med 2013;107: 1053-60.
7. FitzGerald J, Bateman E, Boulet L. Global strategy for asthma management and prevention. *2015*. 2015.
8. Vestbo J, Hurd S S, Agustı A G. Global Strategy for the Diagnosis*,* Management and Prevention of COPD*,* Global Initiative for Chronic Obstructive Lung Disease *(*GOLD*), 2014*. 2015.
9. Barrecheguren M, Esquinas C, Miravitlles M. The asthma-chronic obstructive pulmonary disease overlap syndrome *(*ACOS*):* opportunities and challenges. Curr Opin Pulm Med, 2015;21:74-9.
10. de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease *(*COPD*):* prevalence and risk factors in young, middle-aged and elderly people from the general population. PLoS One 2013; 8:e62985.
11. Soriano J B, Davis K J, Koleman B, Visick G, Mannino D, Pride N B. The proportional Venn diagram of obstructive lung disease*:* two approximations from the United States and the United Kingdom. Chest 2003;124: 474-81.
12. Menezes A M, Montes de Oca M, Péres-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype*:* COPD-asthma. Chest 2014;145:297-304.
13. Hardin M, Silverman E K, Barr R G, et al. The clinical features of the overlap between COPD and asthma. Respir Res 2011;12:127.
14. Perret J L, Dharmage S C, Maatheson M C, et al. The interplay between the effects of lifetime asthma*,* smoking*,* and atopy on fixed airflow obstruction in middle age. Am J Respir Crit Care Med 2013:187:42-8.
15. Vonk J M, Jonqepier H, Panhuysen J I, Schouten J P, Bleecker E R, Postma D S. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. Thorax 2003;58: 322-7.
16. Kiljander T, Helin T, Venho K, Jaakkola A, Lehtimaki L. Prevalence of asthma-COPD overlap syndrome among primary care asthmatics with a smoking history*:* a cross-sectional study. NPJ Prim Care Respir Med 2015;25: 15047.
17. Lange P, Parner J, Vestbo J, Schnohr P, Jansen G. 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339: 1194-200.
18. Brzostek D, Kokot M. Asthma-chronic obstructive pulmonary disease overlap syndrome in Poland. Findings of an epidemiological study. Postepy Dermatol Alergol 2014;31: 372-9.
19. de Marco R, Marcon A, Rossi A, et al. Asthma*,* COPD and overlap syndrome*:* a longitudinal study in young European adults. Eur Respir J 2015;46:671-9.
20. Fabbri L M, Romaqnoli M, Corbetta L, et al. Differences in

airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:418-24.

21. Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. J Asthma 2011;48: 279-85.
22. Kim M A, Noh C S, Chang Y J, et al. Asthma and COPD overlap syndrome is associate*d* with increased risk of hospitalisation. Int J Tuberc Lung Dis 2015;19:864-9.
23. Fu J J, Gibson P G, Simpson J L, McDonald V M. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. Respiration 2014;87: 63-74.
24. Yamauchi Y, Yasunaqa H, Matsui H, et al. Comparison of in-hospital mortality in patients with COPD, asthma and asthma-COPD overlap exacerbations. Respirology 2015;20:940-6.
25. Cosio B G, Soriana J B, Lopez-Campos J L, et al. Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort. Chest 2016;149: 45-52.
26. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms. Thorax 2002;57: 643-8.
27. Siva R, Green R H, Brightling C, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. Eur Respir J 2007;29:906-13.
28. Kim S R, Rhee Y K. Overlap between asthma and COPD*: Where the* two diseases converge. Allergy Asthma Immunol Res 2010;2:209-14.
29. Fu J J, McDonald V M, Gibson P G, Simpson J L. Systemic inflammation in older adults with asthma-COPD overlap syndrome. Allergy Asthma Immunol Res 2014;6: 316-24.
30. Louie S, Zeki A A, Schivo M, et al. The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. Expert Rev Clin Pharmacol 2013;6: 197-219.
31. Koblizek V, Chlumsky J, Zindr V, et al. Chronic Obstructive Pulmonary Disease*:* official diagnosis and treatment guidelines of the Czech Pneumological and Phthisiological Society*;* a novel phenotypic approach *to* COPD with patient-oriented care. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2013;157:189-201.
32. Yalcin A D, Celik B, Yalcin A N. Omalizumab *(*anti-IgE*)* therapy in the asthma-COPD overlap syndrome *(*ACOS*)* and its effects on circulating cytokine levels. Immunopharmacol Immunotoxicol 2016;38:253-6.
33. Tat T S, Cilli A. Omalizumab treatment in asthma-COPD overlap syndrome. J Asthma 2016;53: 1048-50.