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DERLEME / REVIEW

ZOR ASTIM

SEVERE ASTHMA

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ÖZ

Astım havayolu inflamasyonu ile seyreden çeşitli klinik özelliklere sahip bir hastalıktır. Dünyada yaklaşık 300 milyon insanı etkileyen bir inflamatuvar hastalıktır. Astım semptomları alerjenler gibi risk faktörlerinden kaçınarak ve etkili inhaler tedavi ile kontrol altına alınmaktadır. Astımlı hastaların büyük bir çoğunluğu uygun tedavi ile kontrol altına alınmaktadır. Astımlı hastaların % 5-10'unu oluşturan zor astım klinisyenler için tanımı ve tedavisi hala zor bir grubu oluşturmaktadır. İş gücü kaybı ve ekonomik maliyet açısından yüksektir. Uygun tedaviye rağmen bazı olguların kontrolü zorlaşmaktadır. Standart tedavi ile kontrol edilemeyen, steroide bağımlı veya dirençli astım olgularını içermektedir. Astıma bağlı ölümlerin çoğu ağır olan veya stabil olmayan grupta görülmektedir. Heterojen bir hastalık olan astımda farklı fenotipler vardır ve net olarak anlaşılmamıştır. Tedavi yönetimi için multidisipliner yaklaşım gerekmektedir. Ağır astım hastalığın ilk yıllarında veya yıllar sonra gelişebilir. Ağır astımda fenotipe özgü tedaviler günümüzde önem kazanmıştır ve tedavi maliyeti yüksektir. Genetik, çevresel faktörler, yaş ve hastalık süresinin ağır astımda rolü olduğuna dair kanıtlar vardır. Özellikle genetik ve çevresel faktörler ağır astımda önemli rol oynamaktadır. Ağır astım olduğu düşünülen hastalar dikkatle değerlendirilmelidir. Birçok hastalık astımı taklit edebilir. Bu hastalarda öncelikle astım tanısı doğrulanmalıdır. KOAH ve vokal kord disfonksiyonu ayırıcı tanıda özellikle dikkat edilmesi gerekli hastalıklardır. İkinci olarak hastanın tedaviye uyumu gözden geçirilmelidir. Ardından sigara içimi, atopik durum, çalışma ortamı ve aspirin aşırı duyarlılığı gibi faktörler araştırılmalıdır. Aynı zamanda ek hastalıklar gibi astım kontrolünü etkileyebilen durumlar gözden geçirilmelidir. Astımı zorlaştıran durumlar tek tek araştırılmalıdır. Bu derlemede ağır astım tanımı, ayırıcı tanıların dışlanması, fenotipleri ve tedavi yaklaşımları ele alınmıştır.

ANAHTAR KELİMELER: Astım fenotipleri, astım kontrolü, kortikosteroid

ABSTRACT

Asthma is a common inflammatory disease that has wide clinical characteristics of the airway of the lungs. Asthma symptoms can be prevented by avoiding triggers like allergens and by the effective inhaled treatment. The majority of asthma patients can be treated effectively by current medications. Difficult asthma is a distinct entity of asthma, comprising approximately %5-10 of asthmatic patients. Despite the high effective treatment, the patients with asthma have disease that is poorly controlled. Severe asthmatics account for up to half of the cost for asthma. It will include asthma uncontrolled by new standard therapy, steroid dependent, steroid resistant asthma patients. Asthma related deaths are seen especially in severe asthma group. Asthma is a heterogeneous disease, consisting of different phenotypes. It requires multidisciplinary approach for treatment management. Severe asthma may suddenly develop in early time in disease or overtime. There was an evidence that severe asthma related to genetic factors, environmental factors, age, inflammation, duration of disease The genetic and environmental factors may play a role in severe asthma management. Phenotype-targeted therapy has an important role in severe asthma, but it is associated with high treatment costs. At first diagnosis of asthma must be confirmed COPD and vocal cord dysfunction is needed to be particular interest in differential diagnosis. Triggering factors such as smoking, atopy, work place condition and aspirin hypersensitivity should be evaluated. Comorbidities that may affect asthma should be considered. This review examines the definition of asthma, its differential diagnosis, phenotypes and available treatment options.

KEYWORDS: Asthma phenotypes, asthma control, corticosteroid

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hypersensitivity. It is estimated to affect almost 300 million people worldwide (1). There is a significant sub-group of asthma patients who cannot be treated despite the use of currently available effective medications. This sub-group, referred as having severe asthma, accounts for almost 10% of all asthmatic patients. A previous Turkish study reported that 7% of all asthma patients have severe asthma (2). Treatment approaches to severe asthma are controversial and healthcare costs represent a major burden.

DEFINITION

Various definitions have been used to describe severe asthma. Simply, it can be defined as asthma that remains symptomatic despite appropriate and sufficient therapy. ATS/ERS Task Force defines severe asthma as asthma that requires treatment with a high dose inhaled medication plus at least one controller (long-acting beta agonist, leukotriene receptor antagonist, teophylline and/or systemic corticosteroid) to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this therapy. Presence of at least one of the criteria listed under high dose therapy is considered to indicate severe asthma (**Table I**). Moreover, patients who do not meet any of these criteria but become uncontrolled at lower corticosteroid doses are also considered to have severe asthma (3).

Table 1: Diagnostic Criteria for Uncontrolled Asthma

Poor symptom control: ACQ*> 1.5 or ACT **< 19 (or "not well controlled" by National Asthma Education and prevention Programme/Global Initiative for Asthma (NAEPP/GINA) guidelines over the 3 months of evaluation). **Frequent exacerbations:** Two or more cycles of systemic steroids (>3 days each) in the previous year. **Severe exacerbations:** At least one hospitalization, intensive care unit stay or mechanical ventilation need in the previous year. **Airflow limitation:** FEV_1 < 80% of predicted (provided that FEV_1/FVC is less than the lower limit of normal) *ACQ: Asthma Control Questionnaire,**ACT: Asthma Control Test

Severe asthma should be addressed after differentiating two distinct patient groups. The first group, so called "problematic patients", involves those who have received an incorrect diagnosis, who are noncompliant, whose asthma is accompanied by untreated comorbidities, or who are not being regularly followed-up by a pulmonologist. The second group involves patients with treatment-resistant asthma (whose asthma cannot be controlled despite high-dose standard therapy or can only be controlled at high doses). The term "difficult asthma", on the other hand, is used to describe the patients who received a definitive diagnosis of asthma but could not be controlled despite regular follow-up by an asthma specialist for at least 3 months.

PATHOPHYSIOLOGY

Asthma is an inflammatory disease of the airways and several mediators play roles in asthma pathophysiology. Symptoms may be intermittent, but airway inflammation is permanent. Mediators involved in asthma pathogenesis include chemokines, cysteinyl leukotrienes, cytokines such as IL- 1β, TNF-α, GM-CSF, IL-4, IL-5 and IL-13, histamine, nitric oxide and prostaglandin D2. Activated mast cells, activated eosinophils, and an increase in the receptors of T helper and natural killer (NK) T cells play roles in the inflammation associated with asthma (4, 5). Inflammation in severe asthma is measured based on the number of cells in sputum induced from the airways, as well as through endobronchial biopsies and bronchoalveolar lavage. Based on the predominant cell type, inflammatory asthma has been categorized into three different phenotypes as eosinophilic, neutrophilic, and/or paucigranulocytic (6). The concomitant presence of eosinophilic and neutrophilic inflammation has been associated with severe disease (7). Despite being on high dose of corticosteroids, eosinophil and neutrophil numbers show variability in the sputum of severe asthma patients. FENO was also found to be sensitive as an indicator of asthma activity and a marker of inflammatory cell density (8, 9).

In addition to increased inflammatory response, airways of asthmatic patients go through structural changes called airway remodeling (10). A part of these changes has been associated with the severity of asthma and these changes result in relatively irreversible obstruction of the airways. Asthmatic patients develop subepithelial fibrosis. Increased airway smooth muscle, blood vessel proliferation and increased mucus secretion are also observed.

CONFIRMING THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The evaluation should start with a comprehensive medical history and identification of the symptoms. A good anamnesis showing the presence of symptoms such as episodes of shortness of breath, wheezing, cough and chest tightness, along with physical examination findings and demonstration of reversible airway obstruction are often sufficient to establish the diagnosis. Normal physical examination findings or pulmonary function test results should not exclude the diagnosis of asthma (1). As much as 12-30% of patients with severe asthma are indeed misdiagnosed (11, 12). In patients who do not respond to treatment, there are several confounding diseases to be considered for differential diagnosis of asthma (1, 3) (**Table II**). These diseases with similar symptoms should be excluded.

Table 2: Differential Diagnosis in Severe Asthma

Vocal cord dysfunction	Hypersensitivity pneumonia
COPD	Hypereosinophilic syndromes
Panic attack	Pulmonary embolism
Bronchiolitis obliterans	Herpetic tracheobronchitis
Congestive heart failure	Endobronchial lesion/foreign body
Drug-related adverse effects (e.g.: ACEI-related cough)	Allergic bronchopulmonary aspergillosis (ABPA)
Bronchiectasis/cystic fibrosis	Churg Strauss Syndrome (CSS)

TRIGGERS AND COMORBIDITIES

Triggers and untreated comorbidities are other important aspects of evaluation (1). Triggers of asthma are listed in (**Table III**).

Table 3: Triggers in Asthma

ENVIRONMENTAL FACTORS	Allergens	Indoor: in-house mites, pets (cats, dogs), cockroach and fungus
		Outdoor: Pollens and fungus
	Infections: Viral agents in particular	
	Occupational sensitizers	
	Smoking: Both active and passive smokers	
	Air pollution: Indoor and outdoor air pollution	
	Diet	

While the relation of allergy and atopy with asthma is well-known, previous large-scale studies less commonly associated allergy with severe asthma than mild asthma (13). In ENFUMOSA trial, sensitivity to inhaled allergens was found to be comparable between patients with severe and mild-to-moderate asthma, but still at a considerably high rate of 55% (14). On the other hand, severe asthma can coexist with rhinosinusitis in as much as 75-80% of the cases (15).

Smoking is associated with increases in asthma symptoms, exacerbations and hospitalization. Smoking causes corticosteroid resistance. In asthma patients, smoking cessation was shown to improve lung functions and reduce airway inflammation. Avoiding environmental exposure to tobacco smoke was also associated with improved asthma control (2, 16).

Untreated comorbidities result in uncontrolled asthma.

Gastro-esophageal reflux (GER) is present in as much as 60–80% of asthma patients. However, trials did not indicate that antireflux therapy provides the expected improvement in asthma control (17, 18). Although the impact of treatment of sinusitis and GER on asthma control is not clear, when these comorbidities are identified, they should be treated as appropriate.

Prevalence of obesity and asthma has shown a parallel increase over the recent years, which suggests that these two conditions may be epidemiologically related. Studies show that body mass index (BMI) above 30 increases the risk of asthma by 2.7-folds (19,20).

Psychological factors are also involved in uncontrolled asthma. Anxiety and depression have been observed at varying rates (25-49%) among patients with severe asthma (21). However, the impact of treatment of these conditions on asthma control is not clear.

Uncontrolled asthma is also common among individuals with obstructive sleep apnea. Aspirin, beta-blockers and angiotensin converting enzyme inhibitors trigger asthma exacerbations in patients who are sensitive to non-steroidal anti-inflammatory drugs. Asthma control gets difficult also during premenstruation, but severe exacerbations rarely develop during this period. Careful investigation of the comorbidities and treatment planning play crucial roles in asthma control.

TREATMENT COMPLIANCE

In patients who fail to respond to standard therapies, the first action should be to confirm asthma diagnosis. Then, treatment compliance and symptom triggers should be investigated and differential diagnoses should be elaborated. Nevertheless, treatment noncompliance should always be kept in mind as one of the most significant underlying causes of uncontrolled asthma. Factors with an impact on treatment noncompliance include use of incorrect doses by the patients or incorrect drug administration techniques, patients' reluctance to use the medications in order to avoid side effects, their lack of information and cultural differences (1). At each visit, patients should be evaluated by pulmonologists with respect to the use of inhaler device and observed deficiencies or errors should be corrected. Patients should be informed in detail and trained about the correct use of their medications.

SEVERE ASTHMA PHENOTYPES

Phenotype is defined as the observable physical characteristics of an organism, as determined by the interactions between genetic makeup and the environment. The recently emerging concept of phenotype-based therapy set the basis for more detailed phenotyping studies. Severe Asthma Research Program (SARP) classified adult asthma patients into five clusters based on clinical characteristics. These clusters included three groups of early-onset mild, moderate and severe atopic asthma (based on lung function, medication use and frequency of exacerbations). One of the remaining two groups included females with late-onset severe asthma characterized by moderate FEV1 decline and frequent oral corticosteroid use, while the second group involved individuals with late-onset but long-term, very severe, less atopic asthma characterized by less reversible airflow limitation (22). Analysis of another adult asthma cohort defined the following four clusters based on sputum eosinophil count: early-onset atopic-asthma, obese non-eosinophilic asthma, early-onset symptom predominant-asthma, and a later onset inflammation predominant asthma (23).

TREATMENT OPTIONS

Corticosteroids: Corticosteroid-insensitivity, characterized by asthma uncontrolled under corticosteroid therapy or asthma deterioration on tapering or cessation of corticosteroids, also indicates severe asthma. Thus, although corticosteroids are the building blocks of treatment for milder forms of asthma, molecular-targeted alternative therapies may be required in severe asthma to control inflammation and improve corticosteroid insensitivity. Severe asthmatics are often referred to as corticosteroid-dependent, refractory or corticosteroid-insensitive asthmatics. In 30% of adult patients with severe asthma, oral corticosteroids (OCS) are required in addition to ICSs to maintain asthma control (13, 14). Corticosteroid insensitivity in adults has been associated with comorbidities such as obesity, smoking, low vitamin D levels, and non-eosinophilic inflammation (low-Th2 inflammation) (24, 25).

Standard stepwise treatment approach has also been recommended for severe asthma. Fixed-dose combination of inhaled steroid and formoterol is recommended both as maintenance and rescue therapy. SMART studies including tens of thousands of patients demonstrated a reduction in the frequency of asthma exacerbations among patients treated with fixed-dose combinations (26, 27). Studies of intramuscular triamcinolone injection reported improved control of asthma, a reduction in the number of sputum eosinophils and an improvement in asthma exacerbations (28, 29). Addition of a leukotriene receptor antagonist (LTRA) to inhaled steroids provided clinical improvement in studies of patients with severe asthma. In a study comparing addition of a long-acting beta-agonist or a LTRA on top of inhaled steroid therapy, long-acting beta-agonists were associated with improved efficacy (30).

Teophylline: In studies including patients with moderate asthma, teophylline improved asthma control when added to steroids (31). In the smoking asthmatics, addition of teophylline to low-dose inhaled steroid therapy improved asthma control. These findings were attributed to teophylline's ability to improve corticosteroid insensitivity (32, 33).

Tiotropium: Tiotropium is a long-acting inhaled anticholinergic bronchodilator, and its efficacy has been investigated in clinical trials. In a large-scale study, tiotropium added to standard combination therapy provided improvements in FEV1, and reductions in exacerbations and use of short-acting beta-agonists (34). Tiotropium resulted noninferiorly to salmeterol in patients with moderate to severe asthma who were poorly controlled by ICS or ICS/salmeterol (46).

Anti Ig-E: Omalizumab is a monoclonal antibody used for the treatment of patients with severe allergic asthma. Asthma patients aged ≥ 12 years, having perennial allergy and serum IgE levels of 30-1500 IU/mL are eligible to receive omalizumab at doses calculated based on the patient's weight and IgE level. Treatment response should first be assessed on the 16th week of therapy, but some patients may respond later (35). Studies associated omalizumab with reduced need for rescue medications, significant improvements in the symptoms and FEV1, and reductions in emergency admissions and exacerbations (36, 37). Except anaphylaxis (1/1000), omalizumab did not result in marked side effects compared to placebo.

Anti-Interleukin 5: Mepolizumab is used for asthma patients aged ≥12 years with severe eosinophilic asthma that is uncontrolled . A multi-central study showed that the IL-5 antibody mepolizumab significantly reduced exacerbations in eosinophilic asthma patients with frequent exacerbations, in the absence of significant improvements in symptoms, quality of life scores and pulmonary functions (44). Reslizumab is suggested for patients aged ≥12 with severe eosinophilic asthma that is poorly controlled on step 4 treatment (47).

Macrolides: antibiotics were shown to have anti-inflammatory activity in addition to their antimicrobial effects, and they were reported to be effective in the treatment of chronic neutrophilic airway diseases. A previous meta-analysis showed that long-term use of macrolides on top of background therapy provided improvements in symptoms, quality of life, PEF values and airway hypersensitivity in patients with uncontrolled asthma (38). Brusselle et al. investigated the effects of 26-weeks long, three times a week 250 mg azithromycin therapy primarily on the frequency of asthma attacks and respiratory infections. Their findings indicated that, when added to background therapies, 6-months of macrolide therapy did not reduce the frequency of exacerbations or lower respiratory tract infections. On the other hand, a significant reduction was recorded in the frequency of exacerbations in a sub-group of patients with noneosinophilic asthma (39). There is insufficient data on addition of macrolide to the treatment of severe asthma.
Antifungal agents: The use of Allergic Bronchopulmonary Aspergillosis (ABPA) has also been recommended.

Anti-TNF: Anti-TNF medications have an established place in inflammatory diseases, and they were investigated in several trials on asthma patients. While the study of Berry et al. demonstrated improvements in asthma control questionnaire and FEV1 values, Morjoria et al. reported improvement in asthma control test scores but other parameters were comparable to placebo in their study (40, 41). A placebo-controlled trial, on the other hand, did not show any significant improvement in pre-bronchodilator FEV1 percentage, asthma control questionnaire, asthma exacerbations and bronchial hyperreactivity after 12 weeks of therapy (42). Thus, the role of anti-TNF therapy in asthma remains to be clarified.

Bronchial thermoplasty: Chronic airway inflammation and remodeling are prominent in severe asthma patients. Bronchial thermoplasty is a method developed to reduce the airway smooth muscles. A total number of 288 patients were enrolled to a randomized controlled trial performed in 2010, and significant improvements were observed in the asthma quality of life scores of 79% and 64% of the patients who underwent bronchial thermoplasty and placebo, respectively. Bronchial thermoplasty reduced the number of asthma exacerbations, improved asthma-

specific quality of life scores, and decreased the number of school- or working-days lost to asthma (43). However, it is currently unclear which asthma phenotype can benefit from bronchial thermoplasty.

New Treatments: IL-4 and IL-13 are two other cytokines that are important targets of therapy. Both cytokines essentially originate from Th2 lymphocytes and play crucial roles in IgE production (atopy) and remodeling. An IL-13 antagonist, lebrikizumab significantly improved FEV1 in previous trial and this improvement was more pronounced in patients with elevated serum periostin levels (45).

CONCLUSION

Despite currently available standard therapies, disease control still presents an important challenge in the group of treatment-resistant severe asthma patients. Treatment costs are also high in this patient group. Patients' compliance to treatment should be questioned first, and attention must be given to exclude other possible diagnoses. Efficacies of the new alternative treatments, which were developed based on phenotypic characteristics of this treatment-resistant patient group, should be established in studies including large patient populations.

REFERENCES

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Revised 2017 available from http://www.ginasthma.org

2. Bavbek S, Misirligil Z; Study Group. A breath for health: an exploratory study in severe asthma patients in Turkey. Allergy 2008;63(9): 1218-27.

3. Chung KF , Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43(2):343-73.

4. Bousquet J, Jeffery PK, Busse WW, et al. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000;161:1720-45.

5. Miller AL, Lukacs NW. Chemokine receptors: understanding their role in asthmatic disease. Immunol Allergy Clin North Am 2004;24:667-83, vii.

6. Simpson JL, Scott RJ, Boyle MJ, et al. Differential proteolytic enzyme activity in eosinophillic and neutrophillic asthma. Am J Respir Crit Care Med 2005;172:559-65.

7. Hastie AT, Moore WC, Meyers DA, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. J Allergy Clin Immunol 2010; 125: 1028–1036

8. Kharitonov SA. Exhaled nitric oxide and carbon monoxide in asthma. Eur Respir Rev 1999;68:212-18.

9. Turktas H, Oguzulgen K, Kokturk N, et al. Correlation of exhaled nitric oxide levels and airway inflammation markers in stable asthmatic patients. J Asthma 2003;40:425-30.

10. Vignola AM, Mirabella F, Costanzo G, et al. Airway remodeling in asthma. Chest 2003;123(3 Suppl):417S-22S

11. Robinson DS, Campbell DA, Durham SR, et al. Systematic assessment of difficult-to-treat asthma. Eur Respir J 2003; 22: 478–483.

12. Aaron SD, Vandemheen KL, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults. CMAJ 2008; 179: 1121–1131.

13. Moore WC, Bleecker ER, Curran-Everett D, 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; 119:405–413.

14. The ENFUMOSA cross-sectional Europe an multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J 2003;22(3):470-7.

15. Ten Brinke A, Grootendorst DC, Schmidt JT, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. J Allergy Clin Immunol 2002; 109: 621–626.

16. Chaudhuri R, Livingston E, McMahon AD, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med 2006; 174: 127–133

17. Good JT Jr, Kolakowski CA, Groshong SD, et al. Refractory asthma: importance of bronchoscopy to identify phenotypes and direct therapy. Chest 2012; 141: 599–606.

18. Mastronarde JG, Anthonisen NR, Castro M, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med 2009; 360: 1487–1499.

19. Holguin F, Bleecker ER, Busse WW, et al. Obesity and asthma: an association modified by age of asthma onset. J Allergy Clin Immunol 2011;127(6):148693

20. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006; 27: 495–503

21. Vamos M, Kolbe J. Psychological factors in severe chronic asthma. Aust NZ J Psychiatry 1999; 33: 538–544

22. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 2010; 181: 315–323.

23. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178: 218–224.

24. Sutherland ER, Goleva E, Strand M, et al. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med 2008; 178: 682–687.

25. Berry M, Morgan A, Shaw DE, et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. Thorax 2007; 62: 1043–1049

26. Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368(9537):74453.

27. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004;20(9):140318.

28. ten Brinke A, Zwinderman AH, Sterk PJ, et al. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. Am J Respir Crit Care Med 2004; 170: 601–605.

29. Ogirala RG, Aldrich TK, Prezant DJ, et al. High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. N Engl J Med 1991; 324: 585–589

30. Ducharme FM, Lasserson TJ, Cates CJ. Longacting beta2agonists versus antileukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev 2006(4):CD003137.

31. Evans DJ, Taylor DA, Zetterstrom O, et al. A comparison of lowdose inhaled budesonide plus theophylline and highdose inhaled budesonide for moderate asthma. N Engl J Med1997;337(20):14128

32. Spears M, Donnelly I, Jolly L, et al. Effect of lowdose theophylline plus beclometasone on lung function in smokers with asthma: a pilot study. Eur Respir J 2009;33(5):10107.

33. Barnes PJ. Theophylline. Am J Respir Crti Care Med 2013:188;9016

34. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012;367(13):1198207.

35. Bousquet J, Siergiejko Z, Swiebocka E, et al. Persistency of response to omalizumab therapy in severe allergic (Ig-Emediated) asthma. Allergy 2011;66(5):6718.

36. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 2005;60(3):3028.

37. Schumann C, Kropf C, Wibmer T, et al. Omalizumab in patients with severe asthma: the XCLUSIVE study. Clin Respir J 2012;6(4):21527.

38. Reiter J, Demirel N, Mendy A, et al. Macrolides for the longterm management of asthma a metaanalysis of randomized clinical trials. Allergy 2013;68(8):10409.

39. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013 Apr;68(4):3229.

40. Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factoralpha in refractory asthma. N Engl J Med 2006;354(7):697708.

41. Morjaria JB, Chauhan AJ, Babu KS, et al. The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. Thorax 2008;63(7):58491.

42. Holgate ST, Noonan M, Chanez P, et al. Efficacy and safety of etanercept in moderatetosevere asthma: a randomised, controlled trial. Eur Respir J 2011;37(6):13529

43. Castro M , Rubin AS , Laviolette M, et al ; AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial . Am J Respir Crit Care Med . 2010 ; 181 (2): 116 - 124

44. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380(9842):651-9.

45. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med 2011;365(12):1088-98.

46. Rodrigo GJ, Castro-Rodríguez JA What is the role of tiotropium in asthma?: a systematic review with meta-analysis. Chest. 2015 Feb;147(2):388-39

47. Castro, M, Zangrilli, J, Wechsler, ME. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015; 3: 355–366