Journal of Allergy & Therapy
ISSN: 2155-6121

Bakakos and Loukides, J Allergy Ther 2015, 6:6
DOI: 10.4172/2155-6121.1000223

Review Open Access

Severe Asthma: Anti-IgE or Anti-IL-5?

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Received date: October 07, 2015, **Accepted date:** November 09, 2015, **Published date:** November 15, 2015

Severe Asthma: Anti-IgE or Anti-IL-5?

Asthma is a common disease affecting more than 300 million people worldwide [1]. According to the recent ERS/ATS consensus severe asthma is defined as asthma that requires treatment with high dose Inhaled corticosteroids (ICS) plus one more controller (and/or oral corticosteroids) in order to be controlled or remains uncontrolled despite the above treatment or becomes uncontrolled with the reduction of high dose ICS or oral corticosteroids [2]. It is a prerequisite that the correct diagnosis of asthma has been confirmed and comorbidities have been identified and treated properly [2]. It is also extremely important to check inhaler technique and ensure good adherence to treatment. Current GINA document suggests that a referral to a specialist with expertise in the management of severe asthma is strongly encouraged for patients not controlled with treatment step 3 [1]. Severe asthma, although accounting for less than 5% of the total asthma population, is responsible for more than 90% of the disease cost, taking into consideration medication needs and flares that require hospitalization or unscheduled visits to the doctor or to the emergency department [2,3]. Accordingly, it is recognized as a significant unmet need.

The options provided for treatment step 5 (GINA) are anti-IgE and oral corticosteroids. The latter are associated with many and sometimes detrimental adverse effects and the lower possible dose is recommended (ideally <7.5 mg prednisolone/day) [1]. Anti-IgE (omalizumab) is the recommended treatment for allergic asthma and this treatment has been associated with reduction of exacerbations and improvement of quality of life [4,5]. New treatments are being tested and are becoming available for this population of severe asthmatics. The majority refers to monoclonal antibodies. The most recent one is anti-IL-5 (mepolizumab), a monoclonal antibody against IL-5 which was found to be particularly effective in severe eosinophilic asthma. In the first studies of mepolizumab eosinophilia was defined as sputum eosinophils >3% despite regular anti-asthma treatment [6,7]. However, most recent studies demonstrated that the definition of eosinophilic asthma was based upon blood eosinophil count. The cut-off point was set to 300 cells per microliter. Using this cut-off level (or 150 cells per microliter at screening) two large studies evaluated the effect of mepolizumab in severe asthma. In the study by Ortega et al., including 576 patients with recurrent exacerbations despite high doses of ICS and oral corticosteroids (25% of them) mepolizumab significantly reduced exacerbations and improved asthma control according to ACQ-5 [8]. In the study by Bel et al., including 135 patients with eosinophilic asthma that were all receiving oral corticosteroids, mepolizumab had a significant corticosteroid-sparing effect, reduced exacerbations and improved control of asthma symptoms [9].

A reasonable question is whether in a newly encountered case of severe asthma anti-IgE or anti-IL-5 should be the first choice. No studies at the moment have been performed to compare the effect difference of these two antibodies on severe asthma. It is conceivable that in non-allergic eosinophilic asthma there is no place for anti-IgE treatment although occasionally omalizumab has been administered in non-allergic asthmatics based upon local production of IgE [10,11]. But in case of allergic eosinophilic asthma what might be the first treatment?

Mepolizumab almost depletes eosinophils from peripheral blood and significantly reduces them from the airways but also omalizumab reduces sputum and tissue eosinophils, as it has been shown in a lung biopsy study [12,13]. In a pooled analysis from five randomized, double-blind, placebo-controlled studies in patients with moderate-to-severe persistent allergic asthma, omalizumab was associated with significantly reduced post-treatment peripheral blood eosinophil counts. Moreover, the greater reductions were observed in those patients with lower post-treatment free IgE levels [14]. In the EXTRA study including 850 patients evaluating the peripheral blood eosinophil count as predictor of treatment effect of omalizumab, it was found that omalizumab was more effective in reducing exacerbation frequency in the high (>260 cells/μl) compared to the low blood eosinophil group [15]. In the same study, high FeNO and high periostin were also predictors of response to omalizumab treatment [15]. Mepolizumab blocks IL-5 that plays a central role in the proliferation, differentiation and survival of eosinophils, while omalizumab eliminates circulating IgE and downregulates the expression of high affinity FcεRI receptors on effector cells such as basophils, dendritic cells and mast cells [16,17]. It is likely that some patients with severe asthma have been treated with anti-IgE and omalizumab was stopped after 16 weeks due to not favorable effect. In that case mepolizumab may be the choice. In the larger study regarding mepolizumab, the DREAM study involving 621 patients, it was demonstrated that only two variables were associated with efficacy and these were baseline peripheral blood eosinophil count and exacerbation frequency in the previous year. The higher these were, the more effective the treatment was [18]. Accordingly, in a case with very high blood eosinophil counts mepolizumab may be the first choice.

IgE has been shown to increase airway remodeling in asthma through increased airway smooth muscle proliferation and deposition of proinflammatory collagens and fibronectin [19]. Recent studies have shown that long treatment with anti-IgE significantly reduced airway wall thickness and reticular basement membrane thickness within 6 and 12 months and this effect was independent of eosinophilic infiltration [20,21]. Moreover, in another study, it was demonstrated that 48 weeks of treatment with omalizumab resulted in decrease in airway wall thickness as assessed by computed tomography [22]. Accordingly, in a severe asthmatic with persistent airway obstruction possibly associated with airway remodeling, omalizumab may be the first choice. However, it should be stated that in a study examining the effect of anti-IL-5 in bronchial biopsies from 24 atopic asthmatics it was demonstrated that apart from the reduction of the numbers and

the percentage of airway eosinophils expressing mRNA for TGF-β1 (which has been implicated in asthma remodeling) anti-IL-5 was associated with reduction in the expression of tenascin, lumican and procollagen III in the bronchial mucosa Reticular basement membrane (RBM) as well as with reduction of TGF-β1 concentration in BAL [23]. These findings indicate that eosinophils contribute to the remodeling process through the deposition of extracellular matrix proteins in the RBM and that the selective reduction of eosinophils from the airways may have a reversing effect on the remodeling process.

On the other hand, one might postulate that a combination of the two monoclonal antibodies may have a significantly stronger effect on the control of asthma in some severe asthmatic patients. We definitely need studies to prove it, but in the DREAM study IgE concentrations and atopic status at baseline were not associated with the response to mepolizumab, thus potentially differentiating this treatment from omalizumab [18]. The future is linked with the need for direct comparisons of anti-IgE and anti-IL-5 against another along with the search for new biomarkers that will have a better ability to predict response to treatment either alone or in combination with the existing ones.

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