

Editorial

Therapeutic potential of antibodies against interleukin 5 in asthma

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Bronchial asthma is characterized by chronic recruitment of eosinophils in the airways. It has been reported that bronchial eosinophil recruitment and activation may even occur in mild-moderate stable asthma and that bronchial epithelium damage and airway responsiveness may be partially associated with the eosinophilic inflammatory reaction.¹ There is increasing evidence that the eosinophil-rich bronchial inflammation characteristic of asthma is orchestrated, at least partly, by cytokine products of activated T lymphocytes. Of particular interest is T-helper type 2 (Th2) cell-derived interleukin-5 (IL-5).² This cytokine mediates the terminal differentiation of committed eosinophil precursors, activates mature eosinophils, and prolongs their survivals in culture and, presumably, at sites of allergic inflammation.³⁻⁶ IL-5 also selectively enhances eosinophil degranulation, antibody-dependent cytotoxicity,³ and adhesion to vascular endothelium.⁴ Monoclonal antibodies to IL-5 administered to animals with allergic asthma cause long-term inhibition of pulmonary eosinophilia and airway hyperresponsiveness.⁵ Furthermore, mice in which the IL-5 gene has been deleted fail to develop pulmonary eosinophilia and airway hyperresponsiveness after allergen challenge.⁶ By topical instillation of IL-5 into the lower airways, it has been demonstrated that IL-5 acts directly as a chemoattractant for eosinophils recruitment into human airway in asthmatics, and as an activator for the recruiting eosinophils.⁷ Furthermore, it has been reported that IL-5 increases airway responsiveness and infiltration of activated eosinophils into the airway in patients with allergic asthma.⁸

Humanized monoclonal antibodies against IL-5 have been synthesized that allow the role of this cytokine to be studied in individuals with asthma. One such antibody, mepolizumab, is a high-affinity humanized, non-complement-fixing monoclonal antibody (IgG1) specific for human IL-5.⁹ Mepolizumab blocks the binding of human IL-5 to the chain of the IL-5 receptor complex expressed on the eosinophil cell surface.⁹ With these findings in mind, Leckie et al¹⁰ aimed to describe the effect of mepolizumab on blood and sputum eosinophils, and the responses to inhaled allergen in human asthma for the first time about a decade ago. Surprisingly, a single intravenous infusion of mepolizumab, which effectively depleted eosinophils from blood and induced sputum in mild atopic subjects with asthma, had no effect on airway hyperresponsiveness or the late asthmatic reaction to

inhaled allergen challenge.¹⁰ In another study, Flood-Page et al¹¹ have administered three doses of mepolizumab to subjects with mild asthma over a 20-week period to determine its effect on baseline bronchial mucosal eosinophils (and other cell types, including basophils and tissue deposition of major basic protein), and demonstrated that even after three doses of mepolizumab there is residual airway eosinophilia, suggesting that this strategy fails to deplete this cell type in the target organ.

The effect of three intravenous infusions of mepolizumab on clinical outcome measures in patients with asthma experiencing persistent symptoms despite inhaled corticosteroid therapy has been investigated in a multicenter, randomized, double-blind, placebo-controlled study.¹² It was found that despite significant reductions in blood eosinophil numbers and sputum eosinophilia with 250 mg and 750 mg of mepolizumab versus placebo, effects on lung function were minimal and no significant effect was seen on forced expiratory volume in 1 second or symptom scores.¹² The above findings suggest that anti-IL-5 treatment is not effective in improving lung function or symptoms in patients with persistent symptoms despite treatment with inhaled steroids. These findings are in keeping with data from the first exploratory clinical study of mepolizumab treatment, which showed no effect on airway hyperresponsiveness or allergen-induced late responses in patients with mild asthma,¹⁰ and from a study using another humanized anti-IL-5 treatment, which showed no significant effect on lung function in subjects with symptomatic asthma despite inhaled steroids.¹³ The lack of response to anti-IL-5 therapy has been widely interpreted as suggesting that the eosinophil does not contribute significantly to the late asthmatic reaction and has no influence on asthma symptoms and other clinical outcome measures. It should be noted that the abovementioned two studies^{10,11} reporting the effect of

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mepolizumab in asthmatic individuals not receiving inhaled corticosteroid therapy did not show any significant clinical effect but were not suitably powered for efficacy in allergen challenge in a parallel group study design or for efficacy in clinical end points.

Previous studies of mepolizumab treatment in patients with less severe asthma have been too short to evaluate the therapeutic effect on the frequency of exacerbations, and the results of these trials of anti-IL-5 treatment among patients with asthma have been disappointing, however, the two new clinical studies^{14,15} investigating therapeutic effects of mepolizumab treatment showed quite positive results. More recently, Haldar et al¹⁴ have completed a randomized, double-blind, placebo-controlled, parallel-group study of patients who had refractory eosinophilic asthma and a history of recurrent severe exacerbations, and in this study, mepolizumab was found to be associated with significantly fewer severe exacerbations than placebo over the course of 50 weeks and with a significant improvement in the scores on the Asthma Quality of Life Questionnaire. Furthermore, mepolizumab significantly lowered eosinophil counts in the blood and sputum. In another randomized, double-blind, parallel-group trial involving patients with persistent sputum eosinophilia and symptoms despite prednisone treatment, Nair et al¹⁵ have demonstrated that intravenous mepolizumab reduced the number of eosinophils in blood and sputum and was associated with prednisone sparing in patients with asthma who had sputum eosinophilia despite the use of oral prednisone and high-dose inhaled corticosteroid treatment.

Unlike previous studies of anti-IL-5 antibodies,¹⁰⁻¹³ the patients in these two new studies^{14,15} had a highly eosinophilic form of asthma. In these two trials, the selective removal of eosinophils had no effect on other asthma outcomes, such as the forced expiratory volume in 1 second, symptoms, and asthma control. In contrast to the narrow range of effects related to eosinophils in patients receiving mepolizumab, the broader anti-inflammatory effects of systemic corticosteroid significantly improved the outcomes independent of mepolizumab therapy. The results imply that eosinophils are not the only cell involved in the pathogenesis disease, even in patients with severe asthma. These studies clearly confirm that in a subgroup of patients with eosinophilic asthma, eosinophils play a role in exacerbations, and in this subgroup, anti-IL-5 antibody therapy has some clinical benefits.

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