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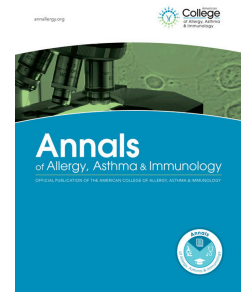
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Letters

Severe uncontrolled eosinophilic asthma, which responded to benralizumab after failure to respond to mepolizumab

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Keywords: anti-IL-5 antibody; Asthma Control Test; benralizumab; blood eosinophil counts; eosinophilic asthma; forced expiratory volume in 1 second; mepolizumab

Abbreviations: ACT: Asthma Control Test; FEV₁: forced expiratory volume in 1 second.

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We present the case of eosinophilic asthma of a 55-year-old female, who was initially diagnosed bronchial asthma by the author in February 2008. The diagnosis was confirmed using the Global Initiative for Asthma guidelines.¹ She showed forced expiratory volume in 1 second (FEV₁) was 63.9 % of the predicted value with an increase of 12.9 % in FEV₁ after 180 µg salbutamol inhaler. She had no history of smoking. She met the American Thoracic Society criteria for a diagnosis of refractory asthma.² She had non-allergic asthma, diagnosed with serum total IgE level 94 IU/mL and negative results of serum specific IgE for common inhaled allergens including mold, and *Dermatophagoides farinae* and *pteronyssinus*. She had occasionally been treated with systemic corticosteroids. Her basal regimen included daily use of budesonide/formoterol 160 µg/4.5 µg inhaler 6 puffs/day and montelukast 10 mg daily.

On February 2, 2018, she visited our clinic because of moderate asthma attack (Figure 1). Peripheral blood eosinophil count was 707/µL, and she was given 250 mg aminophylline and 300 mg hydrocortisone infusion. On February 19, she was given aminophylline and hydrocortisone infusion.

The patient came to our clinic on March 15 as a regular visit. Blood eosinophil count was 867/µL. Percentage of predicted FEV₁ was 48.3 % and Asthma Control Test (ACT) score was 9. She refused oral corticosteroid, but agreed to receive the first subcutaneous administration of 100 mg mepolizumab. On March 22, she visited our clinic because of worsening of asthma symptoms. Blood eosinophil count decreased to 72/µL, however FEV₁ was 46.2 % and ACT score was 9. She was given 250 mg aminophylline infusion. Then, budesonide/formoterol 160 µg/4.5 µg inhaler 8 puffs/day, which is the daily maximum recommended dose in Japan, was prescribed. On April 16, she was given the

second administration of mepolizumab, but required aminophylline infusion. On April 21, because of worsening asthma symptoms, she was given 250 mg aminophylline infusion. On May 14, ACT score was 8, and FEV₁ dropped to 45.8 %. She required 250 mg aminophylline infusion. Her inhaler technique was deemed adequate. She refused to continue mepolizumab, and instead she agreed to have a subcutaneous administration of 30 mg benralizumab. On June 11, FEV₁ improved to 54.7 % and ACT score increased to 21. On July 9, she was given the third administration of benralizumab, and reduced daily dose of budesonide/formoterol 160 µg/4.5 µg inhaler to 4 puffs/day without asthma exacerbations. Since July 9, FEV₁ has been kept above 60.0 %. No side effects have been observed. After the visit on September 3, she was expected to receive benralizumab administration at 8 weeks later. However, she visited our clinic because of asthma symptoms on October 15. On physical examination, slight wheezing during deep breathing on the chest was recorded. Blood eosinophil count, FEV₁ and ACT score was 5/µL, 57.2 % and 23, respectively. She was given the sixth administration of benralizumab, and will be followed up with the administration every 6 weeks.

This is an infrequent case of severe uncontrolled eosinophilic asthma, demonstrating that failure to respond to mepolizumab does not preclude response to benralizumab. Three efficacy endpoints were identified in the patient. Namely, blood eosinophil counts have been approved as a predictive biomarker for the efficacy of anti-IL-5 therapy in patients with eosinophilic asthma,³ and blood eosinophil count was the first criterion. Based on the guideline by the UK National Institute for Health and Care Excellence, which has indicated to use spirometry first to improve diagnosis of asthma,⁴ an improvement of lung function presented the second treatment response criterion. As the

third criterion, we selected the ACT scoring. The scores in the ACT range from 5 (worse control) to 25 (total control), and developmental studies have established the cutoff points for controlled asthma (ACT scores ≥ 20).

After a week of the first administration of mepolizumab, a rapid reduction in peripheral blood eosinophil counts was observed in the patient, but she complained of no improvements of asthma symptoms and required aminophylline infusion. After the second administration, her asthma condition became worse in parallel with dropping of FEV₁ and ACT score, indicating she failed to respond to mepolizumab after 2 doses. However, after switching anti-IL-5 therapy from mepolizumab to benralizumab, her asthma became well controlled.

As IL-5 functions as a central cytokine for activation and recruitment of eosinophils in bronchial asthma, it is not surprising that the number of peripheral blood eosinophil count is an available biomarker for selection of patients who are most likely to benefit from anti-IL-5 treatment.³ However, this case report suggests that cost-effectiveness may only be achieved by identifying responders without the parallel development of biomarkers for clinical application.

It would be difficult to assess the efficacy of mepolizumab after only 2 doses because our patient's asthma was particularly under poor control. However, she refused to continue mepolizumab, and was given benralizumab administration instead. So, potential explanations for our finding are followed. First, benralizumab induces direct, rapid, and nearly complete depletion of eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity.⁶ This mechanism of benralizumab is different than mepolizumab, which targets IL-5 directly and acts through a passive (ie, indirect)

mechanism that ultimately results in eosinophil reduction but not depletion. In fact, it has been shown that mepolizumab produced 100% decrease from baseline for blood eosinophils, but did not deplete airway eosinophils.⁷ On the other hand, a multicenter, double-blind, placebo-controlled phase I study, in which eosinophil counts in bronchial biopsy specimens were determined, showed the photomicrographs demonstrated no eosinophils in the specimens in the benralizumab-treated patients.⁸ Second, one recent case report indicated that there was a rare possibility of worsening of asthma following low-dose mepolizumab treatment, which may be due to local autoimmune mechanisms precipitated by potential inadequate airway levels of anti-IL-5 antibody.⁹ Interestingly, a novel concept of an autoimmune inflammation to the airways of severe eosinophilic asthma has recently been reported.¹⁰

To our best of knowledge, this is the first case report of severe uncontrolled eosinophilic asthma demonstrating failure to respond to mepolizumab does not preclude response to benralizumab.

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Figure Legend

Figure 1 Clinical course of a 55-year-old female patient with eosinophilic asthma. Mepolizumab administration made no improvement in asthma control. However, her asthma condition became to be well controlled with benralizumab administration.

