Successful Treatment of Allergic Bronchopulmonary Aspergillosis With Benralizumab in a Patient Who Did Not Respond to Omalizumab

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Aspergillus is a filamentous hyaline fungus that causes various diseases [1]. Airway and lung invasion by *Aspergillus* species, mostly by *Aspergillus fumigatus*, can result in a complex hypersensitivity reaction known as allergic bronchopulmonary aspergillosis (ABPA). Fungal infection and host immune responses often result in airway injury and fibrosis [2]. The most typical manifestations include chest tightness, dyspnea, elevated IgE levels, eosinophilia, and transient pulmonary infiltrates with moderate fever and brown sputum plugs. Treatment of ABPA is typically based on oral corticosteroids alone or in association with antifungal agents. Favorable clinical progress after concomitant administration of omalizumab has been reported, and, more recently, the use of anti–IL-5 or anti–IL-5 receptor alpha (IL-5Rα) monoclonal antibodies has also proven to be effective [3-6]. However, to date, it is not clear that all patients with ABPA respond to omalizumab, anti–IL-5, or anti–IL-5Rα agents or which criteria should be applied when choosing one treatment over another. We report a case of ABPA that was successfully treated with an anti–IL-5Rα monoclonal antibody (benralizumab) after no response to treatment with anti-IgE antibody (omalizumab).

A 67-year-old man had been followed up until 2005 in our allergy department for nasal polyps and nonallergic asthma that was well controlled with high doses of inhaled corticosteroids and long-acting ß-agonists (LABAs). He did not attend subsequent visits. In 2018, he returned to our clinic because of worsening of his respiratory symptoms over the previous 5 years. He presented with dyspnea on moderate exertion, clear sputum, and nocturnal wheezing that required treatment in the emergency department twice during the previous year owing to more marked clinical deterioration. His most recent pulmonary function values in our department in 2005 were as follows: forced expiratory volume in 1 second (FEV_1) of 3180 mL (90.8%) and forced vital capacity (FVC) of 4380 mL (80%). At his first visit in 2018, his pulmonary function had decreased to FEV_1 of 860 mL (29.2%) and FVC of 2010 mL (53.4%), even though he was receiving high-dose inhaled corticosteroids, LABAs, and inhaled anticholinergics. He again underwent a complete allergology work-up including complete blood count, total and specific IgE determinations, respiratory function tests, and chest computed tomography scan. The result of a skin prick test to *A fumigatus* was positive (wheal >3 mm), and the blood tests revealed specific IgE to *A fumigatus* of 8.41 kU_A/L out of a total IgE of 641 kU/L. Specific IgG to *A fumigatus* was 93 kU_A/L, and the eosinophil count was 590/mL. He had grade 1 nasal polyps, did not complain of nasal congestion or altered smell, and tolerated nonsteroidal anti-inflammatory drugs without problems. The chest computed tomography scan revealed widespread cylindrical, varicose bronchiectasis and mucus plugs, as well as linear and micronodular peribronchial parenchymal opacities in the lower and upper lobes (Supplementary Online Figure). According to these results, the patient met the International Society for Human and Animal Mycology (ISHAM) criteria for ABPA [7]. He started a 6-month treatment schedule with itraconazole and oral prednisone (0.5 mg/kg), which was gradually tapered. Over the 6 months, he was unable to decrease prednisone to below 7 mg/d because of worsening of his symptoms. We then

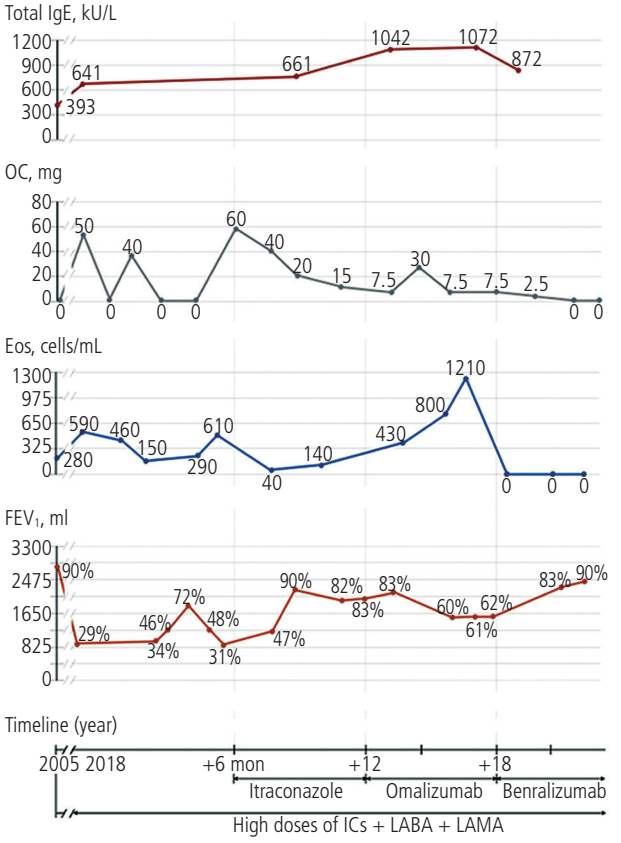

Figure. Oral corticosteroid dose, forced expiratory volume in 1 second, and blood eosinophil count. Eos indicates eosinophils; FEV_1, forced expiratory volume in 1 second; ICs, inhaled corticosteroids; LABA, long-acting-beta agonist; LAMA, long-acting muscarinic antagonist; OC, oral corticosteroids.

initiated treatment with omalizumab 300 mg every 4 weeks. After 6 doses with no improvement in symptoms or pulmonary function, omalizumab was switched to benralizumab 30 mg according to the manufacturer's recommendations. In the first month of treatment, pulmonary function improved, with an FEV_1 of 2630 mL (83%) and FVC of 4070 mL (99%). The patient reported that his symptoms had improved considerably. After the fourth dose of benralizumab, oral corticosteroids were discontinued, and the patient's lung capacity and clinical status remained favorable (Figure).

Conventional treatment of ABPA is based on oral corticosteroids alone or in combination with antifungal agents; this approach usually enables the long-term dose of oral corticosteroids to be reduced. Both antifungal agents and corticosteroids are associated with a well-known range of adverse effects, although this is particularly true of the latter [8,9]. Treatment of ABPA in refractory patients is still largely unexplored. Several reports have shown the effectiveness of omalizumab in ABPA, thus reducing the need for corticosteroids and the number of exacerbations [3]. Emerging anti–IL-5 or anti–IL-5Rα agents are postulated as new treatment options owing to the key role of eosinophils in this disease. Furthermore, treating ABPA with mepolizumab alone or in combination with omalizumab has been documented [4,5]. Benralizumab is a humanized afucosylated monoclonal antibody that binds IL-5Rα, thus leading to apoptosis of eosinophils (and basophils) and reducing T_H2 inflammation. It is indicated as additional maintenance treatment in uncontrolled severe eosinophilic asthma, even in patients receiving high doses of inhaled corticosteroids and LABAs [10]. Its use in ABPA has been reported once [6]. It is not clear why benralizumab was more effective than omalizumab in the present case. Total IgE is known to be a good indicator of disease activity in ABPA. Although the patient had high levels of total IgE, thus making him a good candidate for omalizumab, titers of *Aspergillus*-specific IgE were low with respect to total IgE, and neutralization of IgE antibodies by omalizumab may not contribute in the same magnitude of antagonism as in patients with high *Aspergillus*-specific IgE levels. Likewise, total IgE was determined before treatment with omalizumab, while the patient was receiving oral corticosteroids. Consequently, the real IgE values and the correct dose of omalizumab to be administered may have been underestimated.

The advent of new therapeutic options offers the physician various alternatives for treating the same disease. It is important to know all the immunological mechanisms underlying a specific condition. Although the allergic etiology of ABPA could point physicians to an anti-IgE drug as the first option, treating eosinophilia proved to be effective in the present case.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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