

**Successful treatment of allergic bronchopulmonary aspergillosis with benralizumab after no response to omalizumab**

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*Aspergillus* is a filamentous hyaline fungi culprit of various diseases [1]. Airway and lung invasion caused by *Aspergillus*, mostly by *A. fumigatus*, may result in a complex hypersensitivity reaction known as allergic bronchopulmonary aspergillosis (ABPA). Fungal injury 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 coughing up brown sputum plugs. Typically, ABPA treatment is based on oral glucocorticoids (OC) alone or in association with antifungal agents. In recent years, cases of good clinical evolution after concomitant administration of omalizumab have been described and, more recently, the use of anti-IL-5 or anti-IL-5 receptor alpha (IL-5R $\alpha$ ) monoclonal antibodies have also proven to be effective [3-6]. However, so far, it is not clear that all patients with ABPA respond to omalizumab, anti IL-5 or anti-IL-5R $\alpha$  antibodies or what are the criteria for using one treatment or another. We report a case of ABPA successfully treated with anti-IL-5R $\alpha$  monoclonal antibody (benralizumab) after no response to treatment with anti-immunoglobulin (Ig) E antibody (omalizumab).

A 67-year-old man had been followed up until 2005 in our allergy department for nasal polyps and nonallergic well-controlled asthma with high doses of inhaled corticosteroids and

long-acting-beta agonist (LABA). He did not attend subsequent visits and later on 2018 he came back to our office because of worsening of his respiratory symptoms in the last five years. He presented with dyspnea on moderate exertion, hyaline sputum and nocturnal wheezing requiring to attend the emergency department twice in the last year due to a greater clinical deterioration. His last pulmonary function record in our department in 2005 was forced expiratory volume in 1 second (FEV1) of 3180 mL (90.8%) and forced vital capacity (FVC) of 4380 mL (80%). In his first consultation in 2018 his pulmonary function decreased until FEV1 of 860 mL (29.2%) and FVC of 2010 mL (53.4%) despite being in treatment with high doses of inhaled corticosteroids, LABA and inhaled anticholinergics. A complete allergologic study was then performed again including cell blood count, total and specific IgE determinations, respiratory function tests and chest computed tomography (CT) scan. Skin prick test to *A.fumigatus* were positive (wheal > 3mm) and the blood tests revealed a specific IgE values to *A.fumigatus* of 8.41 kU/L out of a total IgE of 641 kU/L. Specific IgG to *A.fumigatus* was 93 U/L and the level of eosinophils per ml was 590. He had grade I nasal polyps, not reporting nasal congestion or altered smell and he tolerated nonsteroidal anti-inflammatory drugs without problems. Chest CT scan showed cylindrical-varicoid widespread bronchiectasis and mucus plugs, and linear and micronodular peribronchial parenchymal opacities in 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 diagnosis [7]. He started a six months treatment schedule with itraconazole and oral prednisone (0.5 mg/kg) with a gradual tapering. Over these six months he was unable to decrease prednisone below 7 mg per day because of a clinical worsening of his symptoms. We then initiated treatment with Omalizumab 300 mg every 4 weeks. After six doses without any clinical nor pulmonary function improvement omalizumab was

switched to benralizumab 30 mg according the recommendations of the manufacturer. In the first month of treatment his pulmonary function improved showing a FEV1 of 2630 mL (83%) and FVC of 4070 mL (99%), and the patient reported a great clinical improvement. After receiving the fourth dose of benralizumab, oral corticosteroids were removed and good lung capacity and clinical status persisted (Figure 1).

ABPA conventional treatment is based on oral glucocorticoids alone or in combination with antifungal agents which usually allow a reduction in the long-term OC dose. Both antifungal agents and glucocorticoids are associated with a well-known range of side effects, especially the latter [8,9]. Treatment in ABPA refractory patients is still a field to explore. Several reports have shown the effectiveness of omalizumab treatment in ABPA patients reducing the need of corticosteroids and number of exacerbations [3]. The emerging anti-IL-5 or anti-IL-5R $\alpha$  agents are postulated as new possible treatment options due to the key role developed by eosinophils in this disease. Furthermore, treating ABPA with mepolizumab alone or in combination with omalizumab has also been documented [4,5]. Benralizumab is a humanized afucosylate monoclonal antibody that binds IL-5 receptor-alpha leading to eosinophils (and basophils) apoptosis and so, reducing Th2 inflammation. It is indicated as an additional maintenance treatment in severe eosinophilic uncontrolled asthma despite being in treatment with high doses of inhaled corticosteroids and long-acting-beta agonist [10]. Its use in ABPA has been once reported [6]. The reason why benralizumab has been more effective than omalizumab in this case is not entirely clear. Total IgE is known to be a good indicator of disease activity in ABPA. Although the patient had high levels of total IgE which would make him a good candidate for omalizumab, titers of *Aspergillus*-specific IgE regarding total IgE were low 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 determination prior treatment with omalizumab was made while the patient was on oral steroids. That might have underestimated the real IgE values and, therefore, the correct dose of omalizumab to be administered.

The appearance in the market of new therapeutic options offers the physician different alternatives to treat the same disease. It is important to know all the immunological mechanisms underlying one pathology. Although the allergic etiology of ABPA could lead to the idea of an anti-IgE drug as the first option, treating eosinophil has proven to be effective in this case.

#### **conflict of interests**

The authors certify that any of them have any conflict of interests.

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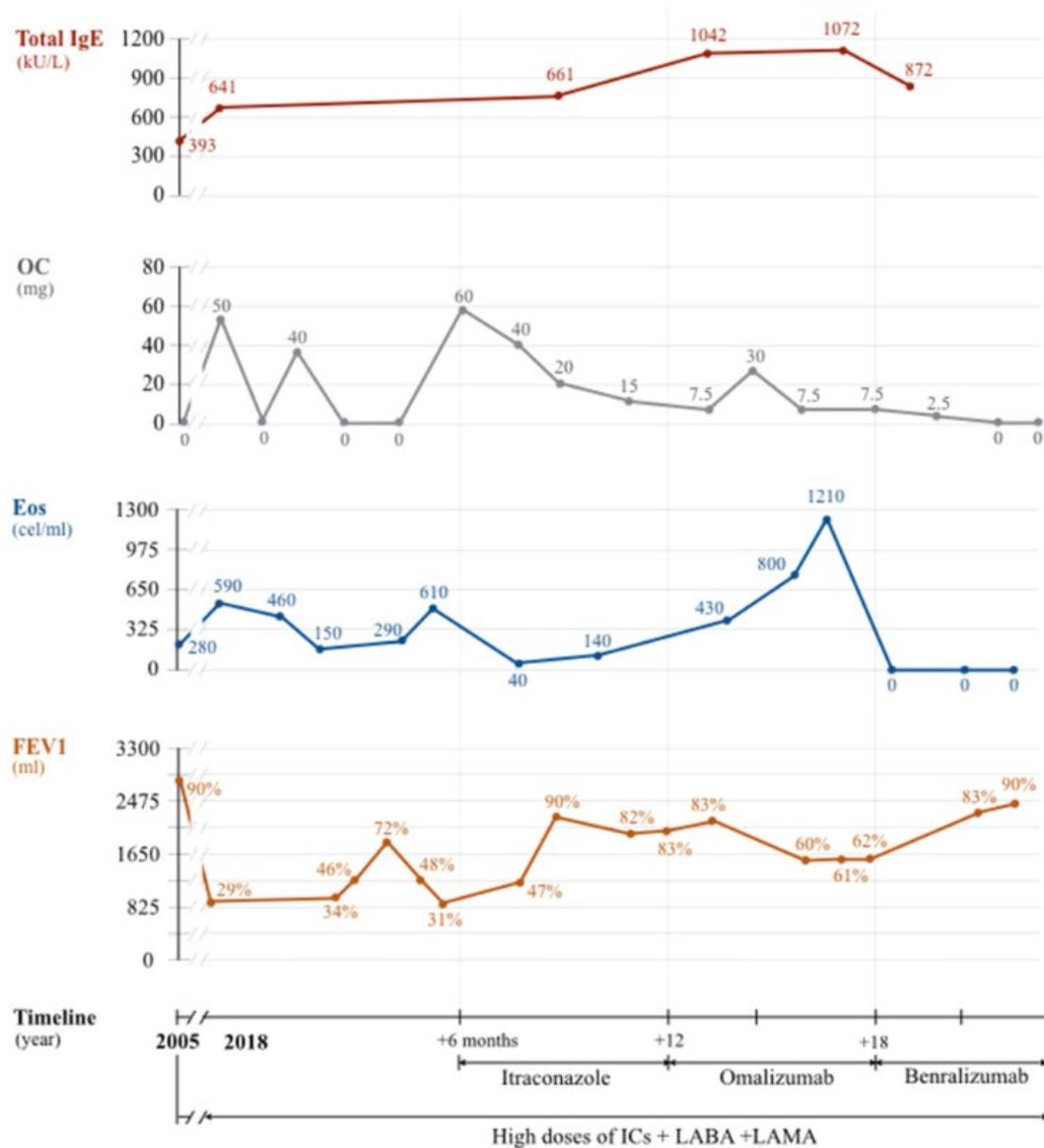
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## FIGURE

**Figure 1 .** Evolution of the oral corticosteroids dose, forced expiratory volume in 1 second and blood eosinophil count.



Eos: eosinophils; FEV1: forced expiratory volume in 1 second; ICs: inhaled corticosteroids;  
LABA: long-acting-beta agonist; LAMA:long-acting anticholinergics; OC: oral

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