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Case Report

Benralizumab and Omalizumab: Dual Biologic Therapy in ABPA and Urticaria

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Abstract

CSU and ABPA seem to have different Type 2 pathogeneses but they can be present at the same time. Here we report a clinical case of a 60-year-old woman affected by ABPA and CSU not controlled by either omalizumab or benralizumab alone. After a 18-month follow-up period of omalizumab and benralizumab combined therapy, both diseases were satisfyingly controlled. The dual biological therapy may be feasible and safe in patients suffering from different diseases contemporarily and uncontrolled by a single therapy. Targeting two different aspects of Type 2 pathogenesis, IgE and IL-5r, provided beneficial control of both diseases with no adverse effects.

Keywords: ABPA; Anti-IgE; Anti-IL-5; Benralizumab; CSU; Omalizumab

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a rare inflammatory lung disease that can be found in patients with bronchial asthma, developing as a complex hypersensitivity reaction to the colonization of the airways by *Aspergillus fumigatus* (AF) [1].

The initial clinical presentation is characterized by frequent asthmatic exacerbations despite therapy, within a framework of poorly reversible bronchial obstruction [2].

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When ABPA is suspected, it is necessary to assess sensitization to AF, either through specific IgE testing or a skin prick test (SPT). Other parameters to evaluate include total IgE levels > 1000 IU/ml, eosinophilia > 500/mcL, and the presence of IgG against AF (>27 mg/L). [3] Actually, recombinant AF antigens rAsp f 1, rAsp f 2, rAsp f 3, rAsp f 4 and rAsp f 6 are used in some countries for detecting immunological sensitization pattern [4].

Once the diagnosis of ABPA is established, the therapeutic approach involves the use of oral glucocorticoids and antifungals, following protocols that entail several months of systemic therapy.

The use of biologic drugs targeting anti-IL-5/IL-5 receptor (IL-5r), anti-IL-4, and anti-IgE has been described in case series for treating ABPA patients. These drugs have shown a potential role in reducing exacerbations, leading to clinical improvement [5].

Chronic spontaneous urticaria (CSU) is a disease characterized by recurrent hives and/or angioedema attacks, its course may be prolonged for years. There are no curative therapies. First line treatment consists of antihistamines which can be augmented by cyclosporine or omalizumab (anti-IgE) if the disease is not controlled [6,7].

CSU and ABPA are not well linked but it is possible to be affected by both.

Case Presentation

In May 2019, a 60-year-old woman came to our attention, for episodes of asthmatic exacerbations. Since 2013, the woman had had a diagnosis of allergic bronchial asthma with sensitization to grasses, pellitory and AF. She had been on therapy with beclomethasone/formoterol 100/6 mcg (2 puffs bd) and montelukast 10 mg/d. Her medical history included CSU, for which she had been receiving omalizumab 300 mg monthly since April 2018. Additionally, she had chronic rhino sinusitis with nasal polyposis, treated with bilateral functional endoscopic sinus surgery in 2018.

Skin prick tests for inhaled allergens showed AF sensitization. Spirometry revealed FEV1 2330 ml (88%), FVC 3230 ml (104%), FEV1/FVC 92%. Total IgE was 945 kUA/L while eosinophils were 400/microliters. A chest computerized tomography (CT) was requested, revealing ground-glass opacities at the left base and cylindrical bronchiectasis in the middle lobe and parahilar region bilaterally. The patient was lost at follow-up during the year of the SARS-CoV-2 pandemic.

She returned in January 2021 due to an asthmatic exacerbation, reporting brownish mucus plugs. Blood tests showed specific IgE for AF at 5.52 kU/L, negative ANCA, and normal alpha-1 antitrypsin. The patient had discontinued omalizumab spontaneously since August 2019, experiencing urticaria recurrence. Spirometry revealed FEV1 920 ml (36%), FVC 1750 ml (57%), FEV1/FVC 68%. She was treated with prednisone 25 mg/d (5 days), beclomethasone/formoterol 200/6 mcg (2 puffs bd), montelukast 10 mg/d, and azithromycin (5 days). After one week, she was reassessed with spirometry, that

Lung function and laboratory findings	May-19	January 2021 (exacerbation)	January 2021 (after 5 days of prednisone)	May 2021 (hospital admission)	July 2021 (introduction of omalizumab)	January 2022 (introduction of benralizumab)	July 2023 (follow up visit with omalizumab and benralizumab)
FEV1 predicted (%)	88	36	64	68	80	70	90
IgE (kUA/L)	945	No data	1078	1044	700	820	792
Eosinophils (cells/microliters)	400	No data	600	870	320	550	20

Table 1: Patient's laboratory and lung function trend.

showed modest improvement, FeNO (Fractional exhaled nitric oxide) 37 ppb; blood tests revealed eosinophils 600/microliters, total IgE 1078 kUA/L, positive IgG for AF. Tiotropium (2 inhalations/day) was added to the treatment.

In May 2021, she was admitted to the Pulmonology Department of Garbagnate Hospital, where several investigations were conducted.

Bronchoscopy with bronchoalveolar lavage revealed bronchial cells with likely hyperplastic-reactive changes, macrophages 89%, lymphocytes 7%, eosinophils 4%, CD4+/CD8+ ratio 0.9. Total IgE was 1044 kUA/L, specific IgE for AF 13.7 kUA/L, Asp f6 7 kUA/L (Asp f4 and Asp f1negative), and positive IgG for AF. Eosinophils were 870/microliters.

A diagnosis of ABPA was made according to modified ISHAM ABPA Working Group criteria. Treatment with voriconazole (200 mg/bd for 4 months) and prednisone (starting dose 75 mg) was initiated and stopped after 3 months. Omalizumab therapy was resumed at 600 mg monthly after about three weeks.

In January 2022, the woman experienced a new asthmatic exacerbation with an eosinophil count of 550/microliters. Benralizumab (anti-IL5-R) was introduced due to the eosinophil level. An attempt to discontinue omalizumab in March 2022 resulted in urticaria relapse.

Since June 2022, she had been on therapy with omalizumab 300 mg monthly and benralizumab 30 mg 8-weekly. In 2023, there was another attempt to discontinue omalizumab, without success. At the last check-up in July 2023, there was no eosinophilia, total IgE was 792 kUA/L, and chest CT showed no more mucus plugs (Table 1). Treatment with benralizumab and omalizumab was continued.

Discussion

The utilization of biologic drugs in Type 2-mediated diseases is steadily increasing. Guidelines indicate parameters to consider when choosing a biologic drug for a specific condition, but there are still no validated recommendations on managing combined biological therapy in a patient with multiple pathologies or inadequate disease control with a single biologic drug. [8] In the case of our patient, omalizumab therapy for urticaria likely provided partial control of asthma. However, the picture was complicated by ABPA, a condition that should be suspected in patients with a history of sensitization to AF who experience frequent asthmatic exacerbations. In addition to first-line therapy with oral corticosteroids and systemic antifungals, biologic drugs have also been reported to be effective. In our clinical scenario, considering the recurrence of asthmatic exacerbations with an increase in eosinophils, benralizumab was initiated to reduce the eosinophilic component, with an excellent respiratory response. Despite recent reports of efficient control of CSU with anti-IL5 drugs in patients with concomitant severe asthma, in our case, the introduction of benralizumab did not show significant improvement in CSU control. [9] Thus, the decision to reintroduce omalizumab therapy (anti-IgE) was made with satisfying control of CSU. Dual biologic therapy was continued. Patient reported improvement of symptoms and quality of life, with no adverse events.

Conclusion

In our knowledge, this is the first reported case of ABPA and CSU treated with benralizumab and omalizumab simultaneously. Targeting two different aspects of type 2 pathogenesis, IgE and IL-5r (and consequently eosinophils), provided beneficial control of ABPA and CSU. Additional research is necessary to evaluate the safety of simultaneous use of different biologic drugs in individuals affected by various diseases in order to implement therapeutic choices.

Conflict of Interest

The authors declare no conflict of interest.

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