Successful treatment with omalizumab of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis: Case reports and literature review

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Clinical implications

- We report 3 cases of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis successfully treated by omalizumab following the failure of first-line therapy.

TO THE EDITOR:

Allergic bronchopulmonary aspergillosis (ABPA) may affect from 1% to 15% of patients with cystic fibrosis (CF).[1] This disease results from hypersensitivity to *Aspergillus* antigens, and afflicted patients may present with airway inflammation, bronchiectasis, and bronchoconstriction. Corticosteroids are the acknowledged first-line therapy for this condition. Itraconazole is often added to therapy if there is a slow or poor response to corticosteroids.

Omalizumab is currently licensed for the treatment of moderate-to-severe uncontrolled allergic asthma and chronic spontaneous urticaria. However, its mechanism of action suggests a possible clinical role in other IgE-mediated disorders, such as ABPA.

In this article, we report 3 cases involving patients with CF with ABPA who were successfully treated with omalizumab.

A 17-year-old male with CF suffered from a persistent dry cough for almost 1 year, with a progressive reduction from 80% to 40% in his predicted FEV_1. His airways were chronically colonized by *Staphylococcus aureus* and recently colonized by *Aspergillus fumigatus*. His last high-resolution computed tomography (HRCT) showed central bronchiectasis in 3 lobes and mucus plugging. His treatment regimen consisted of airways clearance, insulin for CF-related diabetes, rh-DNA-se, inhaled corticosteroids, pancreatic enzymes, ursodeoxycholic acid, and vitamins. The patient was hospitalized for respiratory exacerbation. On this occasion, ABPA was diagnosed on the basis of these criteria: acute clinical deterioration; total IgE level of 1124 IU/mL; positive skin prick test results for *Aspergillus* species (no other sensitivity to environmental allergens); positive specific IgE for *A fumigatus* (16.7 kilounits [kUA]/L); positive precipitating serum antibodies against *A fumigatus*; left mid- and lower-zone consolidations on chest X-ray without any improvement after undergoing standard antibiotic therapy; and peripheral blood eosinophilia.

Therapy was started, first with prednisone and followed by itraconazole, but after 2 months, his clinical conditions showed no improvement. Thus, the patient was treated with omalizumab subcutaneously, with dosages and dosing frequency based on his weight and the initial IgE value. Symptoms and FEV_1 improved after the second omalizumab administration. At week 8 of therapy, his FEV_1 was at 93% predicted, which was his highest in over 2 years, and total IgE level was 363 IU/mL.

The second case was a 28-year-old man with CF who presented with a persistent cough that was ongoing for the last several months and was not responsive to common treatments with inhaled corticosteroids and oral antibiotics. Sputum culture tests showed positivity for *Pseudomonas aeruginosa*, *S aureus*, and *A fumigatus*. HRCT showed central bronchiectasis in 4 lobes, mucus plugging, and air trapping. His treatment regimen consisted of airway clearance, inhaled corticosteroids and antibiotics, pancreatic enzymes, ursodeoxycholic acid, and vitamins. Respiratory function had shown a deterioration over the previous few months, with a progressive reduction in his predicted FEV_1 from 68% to 50% predicted. Diagnostic criteria for ABPA consisted of subacute clinical deterioration; total IgE level of 1105 IU/mL; positive skin prick test results for *Aspergillus* species (no other sensitivity to environmental allergens); positive specific IgE for *A fumigatus* (15.7 kUA/L); positive precipitating serum antibodies against *A fumigatus*; and peripheral blood eosinophilia.

Steroid and antifungal therapy yielded only a partial benefit in terms of slight reduction in daily cough. For this reason, we started omalizumab. At week 8 of therapy, his FEV_1 was at 83% predicted, total IgE level was 301 IU/mL, and his clinical conditions improved.

Finally, an 11-year-old male patient with CF was admitted to our pediatric unit because of acute respiratory failure. Over the last year, we had observed a progressive reduction in his predicted FEV_1 and especially in recent months, his FEV_1 decreased from 60% to 40% predicted. His airways were chronically colonized with *P aeruginosa* and, in the previous 2 months, with *A fumigatus*. His treatment regimen consisted of airway clearance, inhaled corticosteroids and antibiotics, pancreatic enzymes, ursodeoxycholic acid, and vitamins. In his last HRCT, there was some central bronchiectasis in 2 lobes. Diagnostic criteria for ABPA consisted of total IgE level of 1056 IU/mL; positive skin prick test results for *Aspergillus* species (no other sensitivity to environmental allergens); positive specific IgE for *A fumigatus* (14.6 kUA/L); positive airway cultures for *A fumigatus*; new mucoid impaction in right upper and lower lobe on chest radiography that did not disappear with antibiotics; and peripheral blood eosinophilia.

Despite steroid and antifungal therapy administered for a month, he did not improve. Therefore, therapy with omalizumab was started and resulted in significant clinical improvement. After 8 weeks of therapy, his FEV_1 was 68% and total IgE was 456 IU/mL.

The cases are summarized in Table I.

In our series of patients with ABPA complicating CF, poor responses to systemic corticosteroid and antifungal therapies were noted, despite demonstrated sensitivity to itraconazole and therapeutic monitoring showing targeted concentrations. Therefore, omalizumab was administered, and symptoms and lung function improved within 2 to 4 weeks of the first dose. The response persisted over a mean follow-up of 8 months.

TABLE I. Summary of case reports

Characteristic	Case 1	Case 2	Case 3
Age (y)	17	28	11
Sex	Male	Male	Male
Weight (kg)	55	60	38
Genotype	ΔF508/G542X	ΔF508/N1303K	ΔF508/ΔF508
Phenotype	Severe	Severe	Severe
Airways colonization	*S aureus*, *A fumigatus*	*P aeruginosa*, *S aureus*, *A fumigatus*	*P aeruginosa*, *A fumigatus*
Radiographic findings	Left mid- and lower-zone consolidation	Central bronchiectasis in the left midzone	Mucoid impaction in right upper and lower lobes
Last HRCT abnormalities	Central bronchiectasis in 3 lobes and mucus plugging	Central bronchiectasis in 4 lobes, mucus plugging, air trapping	Central bronchiectasis in 2 lobes
FEV_1 deterioration	From 80% to 40%	From 68% to 50%	From 60% to 40%
FEV_1 after omalizumab at week 8	93%	83%	68%
Total IgE before treatment (IU/mL)	1124	1105	1056
Total IgE after treatment (IU/mL)	363	301	456
Blood eosinophils count before treatment (cells/μL)	1430	1250	1050
Calculated dose for omalizumab	600 mg every 2 wk	600 mg every 2 wk	375 mg every 2 wk

Clinical efficacy and immunologic effects of omalizumab in ABPA complicating asthma have already been reported. Tillie-Leblond et al[2] showed a reduction in the number of exacerbations and of the therapeutic load (systemic steroids) in a cohort of 16 omalizumab-treated patients with ABPA, without CF. Voskamp et al[3] treated 13 patients with non-CF ABPA with omalizumab, demonstrating a clinical improvement accompanied by decreased basophil reactivity to *A fumigatus* and FcεR1 and surface-bound IgE levels. Aydin et al[4] evaluated the clinical and functional effectiveness of omalizumab in 14 patients with asthma and ABPA in long-term follow-up demonstrating a clinically important reduction in exacerbations and steroid requirement, and improved asthma symptoms and pulmonary function parameters.

Nevertheless, although omalizumab seems to have a key role in facilitating ABPA control in patients with asthma, there is insufficient published evidence on the use of this drug for ABPA complicating CF, and the long-term benefits are not known. Furthermore, evidence for the use of omalizumab for ABPA in patients with CF is currently limited to data from case reports.[5]

The first case was reported in 2007, when van der Ent et al[6] described a case of a young girl with CF and ABPA who improved after a single dose of omalizumab.[6] Li et al[7] found that, in addition to providing a clinically important reduction in serum IgE levels, exacerbation rates, and steroid requirement, omalizumab treatment facilitated the attenuation of asthma symptoms and improved pulmonary function. A retrospective multicenter observational French study retrieved 32 patients with CF (11 children and 21 adults) who had received omalizumab for more than 3 months in the context of ABPA. Among them, 5 patients were able to discontinue corticosteroids during follow-up and 9 patients were able to reduce their daily dose.[8]

Despite these encouraging results, a Cochrane analysis concluded that omalizumab use in patients with CF and ABPA cannot be unequivocally recommended given the absence of data from randomized trials.[5] Furthermore, there is currently no established recommendation for a standardized omalizumab dose for patients with CF and ABPA, leading to heterogeneity in dosing.[5] A randomized, double-blind, placebo-controlled study (ClinicalTrials.gov Identifier: NCT00787917) designed to assess a range of omalizumab doses in adult patients with CF complicated by ABPA across several European and North American centers was terminated early without publishing interim results after recruitment difficulties.

In contrast with the above-mentioned reports, Ashkenazi et al[9] did not detect any benefits on treating ABPA in CF with omalizumab. However, they administered the drug every month with a lower dosage (maximum 375 mg) compared with our experience.[9]

Regarding the duration of omalizumab use, Wong et al[10] have reported the long-term follow-up of 2 patients with CF and steroid-dependent ABPA who were successfully weaned from long-term corticosteroid therapy when treated with omalizumab. In their cases, monthly omalizumab was administered for 2 years.

In this report, we presented 3 cases in which the failure of first-line therapy was followed by anti-IgE mAb administration, which led to clinical improvement. We administered omalizumab with dosages and dosing frequency based on the patient's weight and the initial IgE values, as recommended for asthma. Our experience supports the safety and efficacy of this therapy. However, as assessed by the Cochrane Collaboration, there remains a need for large prospective randomized controlled trials of anti-IgE therapy in patients with CF and ABPA that assess both clinical and laboratory outcomes, including steroid requirement, ABPA exacerbations, and improvement in lung function.[5] In addition, further data are required to clarify the optimal dose and duration of omalizumab treatment before this expensive therapy can be recommended as a routine treatment approach. In the future, other humanized mAbs might be used in the treatment of ABPA in CF. Mepolizumab, an anti−IL-5 agent used for severe refractory eosinophilic asthma, has been shown to be effective as monotherapy in a 64-year-old woman with ABPA,[11] and in combination with omalizumab in a 58-year-old woman with severe refractory ABPA.[12] Benralizumab, an mAb directed against the alpha chain of the IL-5 receptor (CD125), and dupilumab, an mAb binding to the alpha subunit of the IL-4

receptor (IL-4Rα), may have a potential role in ABPA, but randomized trials are needed.

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