Steroid sparing effect of omalizumab in seropositive allergic bronchopulmonary aspergillosis

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ABSTRACT

Background: Allergic bronchopulmonary aspergillosis (ABPA) is a common serious hypersensitivity reaction to airway colonization with Aspergillus in patients with asthma or cystic fibrosis. While steroids are effective in controlling the respiratory symptoms of ABPA, they have many side effects that make them undesirable for long term use. Antifungals have been used to reduce dependency on systemic steroids but long term use can be limited by side effects and there is the possibility of developing resistance to azoles. Some clinicians have successfully used anti-immunoglobulin E (anti-IgE) therapy in various populations, though it is frequently added to antifungals.

Objective: Further describe the utility of anti-IgE therapy for ABPA for patients unable to tolerate antifungals.

Methods: We describe the case of a patient with serologic ABPA who did not tolerate therapy with antifungals but was able to significantly reduce her average daily steroid use while receiving anti-IgE therapy with omalizumab added to her other respiratory medications.

Results: After therapy with omalizumab, our patient was able to reduce her need for daily corticosteroids by nearly 80%.

Conclusions: Omalizumab may reduce corticosteroid dependence in patients with allergic bronchopulmonary aspergillosis for patients unable to tolerate antifungals, though use may be limited by cost. Additional studies are needed. ClinicalTrial.gov identifier NCT00787917.

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Allergic bronchopulmonary aspergillosis (ABPA) is a serious hypersensitivity reaction to airway colonization with Aspergillus in patients with asthma or cystic fibrosis (CF) and causes difficult-to-control breathing symptoms. In patients with bronchial asthma, the prevalence has been reported in a significant number of patients, ranging from 2% to 32%.1 In many patients, control of their respiratory symptoms becomes dependent on systemic corticosteroids,2 with the accompanying immunosuppressive and metabolic adverse effects. In an effort to decrease patients’ exposure to steroids, many clinicians have turned to antifungal agents,3 or, more recently, anti–immunoglobulin E (anti-IgE) therapy.4–8 We report the case of a patient who did not tolerate therapy with azoles; however, she realized a significant reduction in her daily systemic corticosteroid therapy through the addition of omalizumab. This case is unique in that our patient was not undergoing concurrent antifungal therapy in addition to omalizumab.

Case Presentation

This case was of a 42-year-old woman who was originally diagnosed with ABPA-serologic in 2002 when she was 30 years of age. She was diagnosed at that time based upon a history of asthma, precipitating serum antibodies to Aspergillus fumigatus (IgE total radioallergosorbent test, 2360 IU/mL; A. fumigatus IgE, 7.78; and A. fumigatus IgG, 1.43), a serum IgE level of 2235 IU/mL, and elevated levels of specific anti-Aspergillus antibodies at the time of diagnosis. She underwent a high-resolution computed tomography of the chest, which was normal (all subsequent high-resolution computed tomographies of the chest also were normal). Her pulmonary function test results showed forced vital capacity of 66% predicted and forced expiratory volume in 1 second of 54% predicted with a ratio of 0.69. Starting at the time of diagnosis, the patient was on oral corticosteroid therapy nearly continuously, in addition to tiotropium, fluticasone-salmeterol, montelukast, and albuterol as needed. In November 2006, she was given her first trial of itraconazole 200 mg daily. The patient was able to be weaned off oral steroids but developed elevation of transaminase levels after ~3 months of treatment, which necessitated cessation of itraconazole. A second trial of itraconazole was attempted in November 2008 for 1 month. The patient tolerated this therapy well and was able to...
decrease her prednisone dose to 10 mg every other day. Her pulmonary function test results improved to forced vital capacity of 82% predicted and forced expiratory volume in 1 second of 71% with a ratio of 0.72. She sustained these improvements and was again able to be weaned off steroids in October 2009 for a period of ~11 months. Between October 2010 and March 2011, the patient required oral steroids (20–40 mg daily, with several steroids bursts) to control her ABPA symptoms. She also was hospitalized in December 2010 for an ABPA exacerbation. A third trial of itraconazole was attempted in March 2011, which allowed the patient to come off of daily oral steroids; however, she developed a rash that was suspected to be a drug reaction, and itraconazole was stopped, and the patient required daily oral steroids beginning again in September 2012 and continuing through October 2013.

In October 2013, the patient was started on omalizumab that was dosed as 450 mg subcutaneously every 2 weeks. This has continued to the present time. She required a burst of steroids ~1 month into treatment (November 2013); however, she remained off daily steroids for ~8 months. In May 2014, she was restarted on low-dose maintenance steroids at 10 mg every other day because she began to experience worsening of her respiratory symptoms and had decreasing peak flows.

We calculated the patient’s average daily dose of prednisone during each clinical situation and present these data in Fig. 1. This shows nearly an 80% reduction in the average daily steroid use after the patient was started on omalizumab. IgE levels also decreased and were down to 1172 IU/mL most recently. In addition, there was a marked decrease in unplanned health care utilization after starting omalizumab. Before starting omalizumab, our patient was seeing her allergist or pulmonologist on average approximately once every other month, in addition to multiple emergency department (ED) visits and several hospitalizations. After starting omalizumab, she has had only one ED visit and has seen her allergist only twice over the past 17 months. Both of these visits were scheduled. Although omalizumab is expensive, some of this cost may be offset by decreases in ED visits, hospitalizations, clinic visits, and the patient’s days off work and quality of life. This would be an interesting topic for additional study.

**Discussion**

This case provides additional evidence that both itraconazole and omalizumab have steroid-sparing effects when used for the treatment of ABPA. Itraconazole has
previously been the most commonly used steroid-sparing medication for ABPA9; however, its use can be limited by adverse effects as was the case with our patient and there is concern that there may be increasingazole resistance.10 Elsewhere in the literature, it has been reported that omalizumab can decrease steroid dependence and ABPA exacerbations4–8; however, most of these studies reported on patients with concomitant CF and/or evidence of bronchiectasis. Indeed, Moss9 highlighted the need for separating patients with ABPA based on structural lung disease, because patients with different degrees of structural lung disease may respond differently to therapeutic interventions. Tillie-Leblond et al.7 excluded patients with CF and also had four patients without bronchiectasis; however, the dosages of omalizumab and the IgE levels were not reported for individual patients, so it is difficult to compare their findings with ours.

Brinkmann et al.5 reported a case of a child with CF who remained steroid dependent even after anti-IgE therapy. They postulated that perhaps a higher dose ofomalizumab (dosed based on IgE levels) might have been responsible for the more successful treatment that was observed by Zirbes and Milla.4 Our patient had extremely high IgE levels (as high as 5236 IU/mL before starting omalizumab), so a higher dose of omalizumab was used (450 mg every 2 weeks); however, this dose was not as high as the doses that Novartis Pharmaceuticals (ClinicalTrials.gov identifier NCT00787917) attempted to use in their now terminated clinical trial (doses up to 600 mg per day; the trial was aborted because of difficulty recruiting patients) nor was it as high as the calculated monthly dose of anti-IgE therapy needed to bind >90% of free IgE in the body (0.016 mg/kg * IgE level [IU/mL]). Would our patient be completely steroid free on an increased dose of omalizumab, up to a monthly dose of 6000 mg? We hope to answer this question in the future, and we join others in calling for randomized prospective studies on thesteroid-sparing effects of omalizumab.

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