

Treatment of Allergic Bronchopulmonary Aspergillosis (ABPA) in CF With Anti-IgE Antibody (Omalizumab)

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Summary. Allergic bronchopulmonary aspergillosis (ABPA) results from IgE induced pulmonary response to aspergillus species. Recognition and management of ABPA is challenging in cystic fibrosis (CF) patients because changes in symptoms, lung function and chest radiograph are similar to that seen in CF related pulmonary infection. Standard therapy for ABPA includes systemic steroids and adjunctive use of antifungal agents. Little has been published regarding the use of monoclonal anti-IgE antibody in those with ABPA. We report a CF patient with her third exacerbation of ABPA who was treated with monoclonal anti-IgE (omalizumab) antibody; she had unfavorable side effects with prednisone therapy. This therapy resulted in improvement of pulmonary symptoms and lung function not achieved with antibiotics or prednisone alone. **Pediatr Pulmonol.** 2008; 43:1249–1251. © 2008 Wiley-Liss, Inc.

Key words: cystic fibrosis; allergic bronchopulmonary aspergillosis; monoclonal anti-IgE antibody.

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) prevalence is from 1% to 15%^{1–3} in cystic fibrosis (CF) patients and is an IgE mediated lung disease in response to *Aspergillus* species, most commonly *Aspergillus fumigatus*.^{4–6} Classical diagnostic criteria include: asthma, immediate cutaneous reactivity to *A. fumigatus*, elevated total IgE, and elevated IgE and IgG to *A. fumigatus*.^{4,6} In CF patients, modified criteria are clinical deterioration, radiographic abnormality, IgE > 1,000 IU/ml, immediate cutaneous reactivity and precipitating antibodies to *A. fumigatus*.¹ Systemic corticosteroids are the mainstay of therapy and adjunctive antifungal agents in non-CF patients results in reduced IgE, reduced corticosteroid dose and improved lung function.⁷ Prior successful response to anti-IgE therapy in a pediatric CF patient with ABPA has been published;⁸ we report another pediatric CF patient with positive response to anti-IgE antibody.

CLINICAL REPORT

M.S. is a 13-year-old female with CF (homozygous $\Delta F508$). She was in usual state of health with baseline forced expiratory volume one second (FEV1) 89% predicted and presented at 8 years old with chest tightness and FEV1 of 39% predicted. Evaluation revealed total IgE

level 2,030 IU/ml, immediate cutaneous reactivity to *A. fumigatus*, *A. fumigatus* IgG precipitants and new right upper lobe infiltrate with bronchiectasis consistent with ABPA, requiring 4 months of prednisone for improvement of cough, tightness, IgE and FEV1.

At ages 9 and 10, she had two ABPA exacerbations characterized by increased cough, wheeze, and chest tightness with >2-fold increase in baseline IgE (152–297 IU/ml) requiring 12 months of prednisone with itraconazole (200 mg qd) and 5 months of prednisone respectively. During this period, she had wet cough and was evaluated for infection. Bronchoscopy revealed

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normal flora and laryngeal inflammation consistent with reflux and CAT scan revealed opacification of her sinuses. Sinus surgery revealed purulent mucus growing methicillin resistant *Staphylococcus aureus* (MRSA).

Between 11 and 12 years old, she had symptoms, occasional decreased FEV1 (baseline IgE) transiently responding to antibiotics. Her sputum cultures revealed MRSA and *Pseudomonas aeruginosa*. Other therapies included combination inhaled corticosteroid-long acting beta agonist, reflux, and macrolide therapy. By 13 years old, her cough, wheeze, and chest tightness continued, FEV1 fell from 80% to 57% predicted and IgE was 947 IU/ml. Due to prior prednisone effects glucosuria and mood alteration and recent onset of impaired glucose tolerance, parents were hesitant about the use of prednisone and we started omalizumab 300 mg subcutaneously every 2 weeks.

Symptoms and FEV1 improved after the second omalizumab dose and adjuvant oral antibiotic therapy. At week 11 of therapy (Fig. 1), her FEV1 is at 93% predicted, her highest in over 2 years. She has no wheeze or chest tightness and had not been able to achieve this FEV1 with steroids or antibiotics. She continues to have FEV1 greater than 90% predicted.

DISCUSSION

Our patient was able to achieve her best lung function with the use of omalizumab by week 11. Clinical and lung function improvement was observed 4 h after omalizumab in one CF patient with ABPA.⁸ In asthma patients, symptoms decreased by week 4 of therapy and maximum benefit occurred week 16 of therapy; therefore, it is recommended that patients be treated for a minimum of 16 weeks before deciding that omalizumab is not effective.^{9–12} Although our patient had ABPA exacerbation, other factors such as CF related bacterial infection

and reflux may have been contributors to her respiratory illness.

Although ABPA has specific diagnostic criteria, features of ABPA in CF such as increase sputum, decreased lung function, new infiltrate or bronchiectasis occur with CF bacterial pulmonary infection. In addition, similar immune responses to aspergillus in the absence of ABPA occur in CF patients,⁵ posing diagnostic challenges. Treatment of ABPA relapse in CF should be considered for a >2-fold increase in baseline IgE and therapy failure for CF related bacterial infection. Concomitant therapy for CF related bacterial infection during ABPA exacerbation should be considered for changes such as sputum production and/or leukocytosis,¹ as with our patient (Fig. 1).

The pathogenesis of this disease is not fully understood and is characterized by elevated IgE response. CF patients with ABPA have higher *A. fumigatus* induced Th2 (allergy skewed) T cell response; additionally, B cells of CF ABPA patients had higher *A. fumigatus* specific IgE production versus those without ABPA.^{13–15} Omalizumab reduces unbound (free) IgE concentrations and down-regulates IgE receptors decreasing exacerbations in severe allergic asthma.¹⁶ Because total IgE concentrations can increase 2–5 times baseline during treatment and return to baseline after prolonged discontinuation of therapy,¹⁷ measuring total IgE is impractical for assessing ABPA treatment response on omalizumab. The frequency of anaphylaxis has been reported at 0.2%; our patient had no adverse effects. Prolonged use of prednisone therapy for ABPA may result in glucose intolerance, decreased bone density, and linear growth retardation, for which CF patients are at increased risk.^{18–21} Therefore, omalizumab may be an alternative therapy in CF patients with prior adverse prednisone effects. Given the paucity of information and successful treatment, randomized controlled trials would be needed to determine efficacy in this patient population.

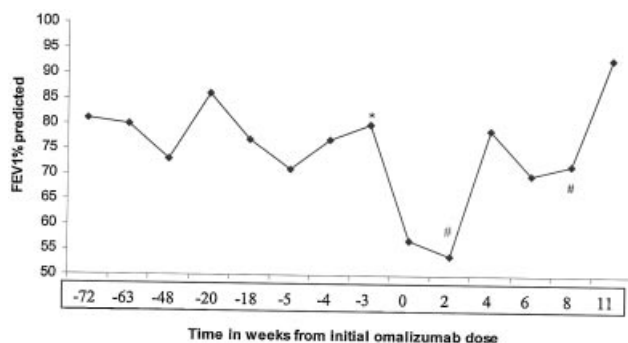


Fig. 1. Shows lung function value FEV1 (forced expiratory volume in one second) in percent predicted expressed as a function of time in weeks from initial omalizumab therapy. (*) IV antibiotic therapy given prior to diagnosis of 3rd ABPA relapse and (#) oral antibiotics given after diagnosis of 3rd ABPA relapse.

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