Case Report

Omalizumab Therapy for Allergic Bronchopulmonary Aspergillosis in Children with Cystic Fibrosis: A Synthesis of Published Evidence

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Summary. Allergic bronchopulmonary aspergillosis (ABPA) complicating cystic fibrosis (CF) is treated with corticosteroids. Since elevated IgE is a cardinal abnormality, anti-IgE has been used sporadically as adjuvant treatment. In eight case reports, 13 children with CF and ABPA received anti-IgE resulting in improved FEV_1, fewer respiratory symptoms and decreased corticosteroid use. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a complication of cystic fibrosis (CF) associated with accelerated lung function decline.[1] It represents a complex immunologic response to *Aspergillus fumigatus* antigens. ABPA diagnosis is based on the presence of: (i) acute or subacute respiratory deterioration that cannot be attributed to another cause; (ii) total serum IgE >500 IU/ml; (iii) positive serum *A. fumigatus*-specific IgE (or immediate cutaneous reactivity); (iv) positive *A. fumigatus*-specific serum precipitins (or IgG); and (v) new/recent abnormalities on chest radiogram (pulmonary infiltrates). Peripheral blood eosinophilia may also be demonstrated. Systemic corticosteroids remain the mainstay of treatment and antifungal agents are added to reduce the aspergillus antigen burden. However, corticosteroid adverse effects have led to the exploration of novel therapeutic interventions.

Omalizumab is a monoclonal antibody (anti-IgE) with established efficacy in severe allergic asthma. Since elevated total IgE is a cardinal abnormality of ABPA, omalizumab has been used sporadically in an effort to decrease corticosteroid dose or totally replace corticosteroids. Although case reports have been published, there are no randomized, placebo-controlled trials evaluating this treatment approach. The current report is a synthesis of the limited published literature on the potential efficacy of omalizumab as treatment for ABPA in children with CF.

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METHODS

Search Strategy

PubMed was searched for articles published in the English language from January 1990 to May 2013, using the following search criteria: "omalizumab" and ("allergic bronchopulmonary aspergillosis" or "aspergillus" or "cystic fibrosis"). Studies were included if they involved

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children (≤18 years old) and provided enough data to calculate changes in forced expiratory volume in 1 sec (FEV_1), in the prevalence of respiratory symptoms and in the frequency of treatment with corticosteroids or antifungals following an omalizumab course. Selected studies were not necessarily randomized and placebo-controlled. Thus, case reports were also considered. Reviews and investigations involving patients >18 years old or subjects with ABPA and asthma (but not CF) were excluded.

Statistical Analysis

FEV_1 and use of maintenance or intermittent systemic corticosteroids were primary efficacy endpoints of the present data synthesis. Secondary endpoints were: presence of persistent respiratory symptoms or recurrent respiratory exacerbations and use of itraconazole.

The mean of the paired differences in FEV_1 (after omalizumab-before omalizumab) and the 95% confidence intervals (mean paired difference $\pm$ t $\times$ standard error of paired differences; degrees of freedom $= N_{pairs} - 1$) were calculated. The 95% confidence intervals for differences in the proportions ($P_2 - P_1$) of subjects receiving maintenance or intermittent corticosteroids (after omalizumab-before omalizumab) were estimated as:

$$\text{lower limit} = (P_2 - P_1) - 1.96 \times \text{standard error of difference} - [(N_1 + N_2)/(2 \times N_1 \times N_2)]$$

$$\text{upper limit} = (P_2 - P_1) + 1.96 \times \text{standard error of difference} + [(N_1 + N_2)/(2 \times N_1 \times N_2)]$$

and standard error $= \sqrt{[P_1(1 - P_1)/N_1 + P_2(1 - P_2)/N_2]}$. Similar calculations were carried out regarding the 95% confidence intervals for differences in the proportions of subjects with persistent or recurrent respiratory symptoms or who were treated with itraconazole (after omalizumab-before omalizumab).

TABLE 1— Characteristics of Patients With Allergic Bronchopulmonary Aspergillosis (ABPA) and Anti-IgE (Omalizumab) Efficacy Endpoints

	Prior to anti-IgE (n = 13) [range]	After anti-IgE (n = 13) [range]	Mean paired difference or difference between proportions of subjects (95% confidence interval) [range]
Age, years	13.3 ± 1.5 [11–16.3]	—	—
Gender, female (% subjects)	4/13 (30.8)	—	—
ABPA duration, years	4.5 ± 2.2 [1.1–10.3]		
Total IgE, IU/ml	1936.7 ± 1459.9 [248–19506]	—	—
Positive specific IgE for aspergillus (% subjects)	10/10 (100)	—	—
Immediate skin reactivity to aspergillus (% subjects)	8/8 (100)		
Positive serum precipitins for Aspergillus (% subjects)	10/11 (90.9)	—	—
Positive serum IgG for aspergillus (% subjects)	3/3 (100)	—	—
Fleeting densities or bronchiectasis on chest X-ray or chest CT scan (%)	7/9 (77.8)	—	—
Eosinophilia (% subjects)	4/4 (100)	—	—
Corticosteroid side effects (% subjects)	9/13 (69.2)	—	—
FEV_1 (% predicted)	71.2 ± 21.7 [36–112]	83.5 ± 17.9 [55–108]	+12.4 (+2.6 to +22.2) [−10 to +38]
Maintenance systemic corticosteroids (% subjects)	7/13 (53.8)	1/13 (7.7)	−46.1(−84.5 to −7.7)
Intermittent systemic corticosteroids (% subjects)	6/13 (46.2)	0/13 (0)	−46.2 (−81 to −11.4)
Recurrent exacerbations (% subjects)	10/13 (76.9)	1/13 (7.7)	− 69.2 (−100 to −31.5)
Persistent symptoms (% subjects)	3/13 (23.1)	0/13 (0)	−23.1 (−53.71 to +7.5)
Use of itraconazole with omalizumab (% subjects)	2/13 (15.4)	2/13 (15.4)	0 (−35.4 to +35.4)

Mean ± standard deviation are provided for continuous variables.

TABLE 2—Summary of Analyzed Case Reports on the Administration of Anti-IgE (Omalizumab) for Allergic Bronchopulmonary Aspergillosis in Children With Cystic Fibrosis

First author, year	No. of patients	Sex	Age at anti-IgE onset (yrs)	ABPA duration prior to anti-IgE (yrs)	Serum IgE (IU/ml)[1]	Prednisone use	Anti-fungal use	Anti-IgE dosage/ duration	Improved persistent symptoms or fewer exacerbations	Prednisone discontinued or decreased	Follow-up after anti-IgE end (m)
Van der Ent, 2007[2]	1	F	12	4	5,200	10–15 mg/day	No	300 mg per 2 wks for 6 wks	Yes	Before anti-IgE initiation	0
Zirbes, 2008[3]	3	M	11.4	4.4	805	40 mg, per other day	Yes, before anti-IgE initiation	300 mg per 2 wks for 18 m	Yes	9 m after anti-IgE initiation	0
		M	11.3	5.3	2,894	1 mg/kg per other day	Yes, before anti-IgE imitiation	375 mg per 2 wks for 18 m	Yes	Before anti-IgE initiation	0
		M	16.3	10.3	530	20 mg, per other day	Yes, before anti-IgE initiation	300 mg per 4 wks for 8 m	Yes	4 m after anti-IgE initiation	0
Kanu, 2008[4]	1	F	13	5	947		Yes, before anti-IgE initiation	300 mg per 2 wks for 11 wks	Yes	Before anti-IgE initiation	0
Lebecque, 2009[5]	2	M	14	3	4,261	Corticosteroid courses for exacerbations	Yes, before anti-IgE initiation	375 mg per 2 wks then per 4 wks for 7.5 m	Yes	Before anti-IgE initiation	4.4
		F	14	3	1,526	Corticosteroid courses for exacerbations	Yes, before anti-IgE initiation	375 mg per 2 wks then per 4 wks for 7.5 m	Yes	Before anti-IgE initiation	4.4
Randhawa, 2009[6]	1	F	11.5	1.1	19,506	10 mg per other day	Yes, during anti-IgE course	375 mg per 2 wks for 6 m	Yes	1 wk after anti-IgE initiation	11
Brinkmann, 2010[7]	1	F	14	4	248	7.5 mg/day (prednisolone)	Yes, before and during anti-IgE course	300 mg per 4 wks for 12 m	Severe exacerbation while on treatment and during steroid taper	Not decreased	0
ElMallah, 2012[8]	2	M	14.5	≥5.5	1,039	Every other day	No	450 mg per 4 wks for 18 m	Yes	4 m after anti-IgE initiation	0
		M	11	2	1,782	Corticosteroid courses for exacerbations	No	450 mg per 2 wks for 12 m	Yes	Before anti-IgE initiation	0
Wong, 2013[9]	2	M	14	5.8	4,388	≤2 mg/kg/day and monthly pulsed intravenous methyl-prednisolone (15 mg/kg/day for 3 days)	Yes, before anti-IgE initiation	300 mg per 4 wks for 24 m	Yes	4.8 m after anti-IgE initiation	0
		M	13.3	4.8	2,884	≤1.5 mg/kg/day and monthly pulsed intravenous methyl-prednisolone (15 mg/kg/day for 3 days)	Yes, before anti-IgE initiation	300 mg per 4 wks for 32 m	Yes	15 m after anti-IgE initiation	0

Antifungal was itraconazole and in one case (Brinkmann) itraconazole or voriconazole.
[1]Most recent value provided by the authors.

RESULTS

Search Results and Characteristics of Included Studies

Twenty-four titles in the English language were retrieved. Fifteen articles were excluded: eight were reviews; two were studies including patients with ABPA and asthma but without CF; four reported omalizumab administration in adult patients with CF and ABPA; one was report of a case with ABPA, intermediate sweat chloride test and only one CF-causing mutation. The remaining nine publications were case reports of children with CF that received omalizumab as treatment for ABPA.[2–10] In two articles, the same two pediatric patients were reported.[5,10] Thus, data from eight publications reporting a total of 13 children with CF and ABPA were analyzed.

Patient characteristics are summarized in Table 1. Criteria for ABPA diagnosis in the presence of CF were fulfilled in all cases.[1] The mean ± standard deviation (range) duration of ABPA by the time that treatment with omalizumab was initiated was 4.5 ± 2.2 (1.1–0.3) years. Prednisone up to 2 mg/kg daily or every other day was used, but in one report[9] monthly pulsed intravenous methylprednisolone (15 mg/kg/day for 3 days) was also administered in an effort to achieve rapid control of ABPA exacerbation. Most patients (69.2%) had experienced adverse effects related to long-term use of corticosteroids prior to omalizumab. In the majority of cases (76.9%), itraconazole (or voriconazole) had been added periodically to systemic corticosteroids. Main characteristics of each of the analyzed case reports are summarized in Table 2.

Data Synthesis

Mean (range) omalizumab dose was 346.2 ± 57.6 (300–450) mg administered every 2–4 weeks for 1.5–32 months (Table 2). Treatment with anti-IgE was initiated with the purpose to either decrease systemic corticosteroid dose (53.8% of patients)[3,6–9] or to control an exacerbation without administering corticosteroid systemically (46.2% of patients).[2–5,8,9] Anti-IgE treatment was related to significant increase in FEV_1 and reduction in proportions of subjects receiving maintenance or intermittent systemic corticosteroids (Table 1 and Fig. 1). Significantly fewer subjects had recurrent respiratory exacerbations after the omalizumab course (Table 1). Use of itraconazole (two cases) did not change. Corticosteroids were discontinued or reduced either prior to omalizumab initiation or 1 week to 15 months later (Table 2). In only 1 of 13 patients, it was not possible to decrease the dose of corticosteroid secondary to relapse of respiratory symptoms. Duration of follow-up after completion of omalizumab treatment was 0–11 months.

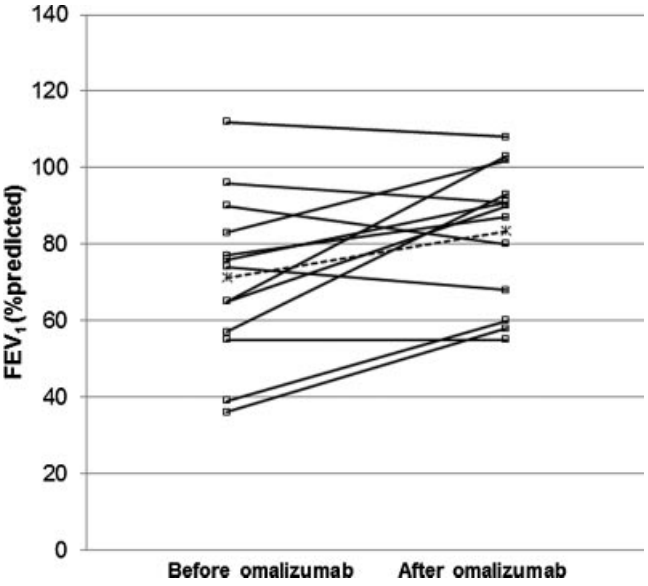

Fig. 1. Forced expiratory volume in 1 sec (FEV_1) for individual patients with cystic fibrosis and allergic bronchopulmonary aspergillosis before and after treatment with anti-IgE (omalizumab). Broken line represents the change in mean FEV_1 for all subjects before and after treatment.

DISCUSSION

In the current data synthesis of published case reports, it has been found that treatment with anti-IgE (omalizumab) is associated with improved expiratory flow function, reduced frequency of respiratory symptoms and decreased use of systemically administered corticosteroids. However, it should be noted that the summarized data resulted from non-randomized, unblinded treatment interventions lacking a comparison, placebo-treated group. An attempt at conducting a randomized, controlled trial was discontinued due to an inability to enroll and maintain subjects in the study (clinicaltrials.gov NCT00787917).

Most children described in the summarized reports had a long-standing diagnosis of ABPA, with recurrent exacerbations, hospitalizations, and prolonged courses of corticosteroids. The majority of them had side effects due to chronic administration of corticosteroids. Several children received adjuvant treatment with itraconazole but without therapeutic success. Omalizumab was administered in an effort to either decrease the dose of maintenance corticosteroids or to control an ABPA exacerbation without using corticosteroids.

The pathogenesis of ABPA remains poorly understood. Patients with ABPA have enhanced Th2 cell response to *A. fumigatus*, increased specific IgE production against A. fumigatus by B-lymphocytes and raised total serum IgE.[1] In some of the reported cases, total IgE was measured following the omalizumab course and was found

persistently elevated.[3] This finding implies that omalizumab blocks the activity of circulating IgE (fewer free molecules), possibly down-regulating the IgE receptors on immune effector cells.[11] Moreover, administration of omalizumab has been accompanied by reduced airway eosinophilia and decreased IL-4+ cells in allergic asthma and these mechanisms of action could be active in ABPA.[12,13]

In conclusion, omalizumab may be an alternative therapy for ABPA in CF patients who fail to respond to systemic corticosteroids or have serious adverse effects. However, a double-blind, randomized, placebo-controlled trial is necessary to establish the efficacy and safety of this novel therapeutic intervention for ABPA.

REFERENCES

1. Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, Denning DW, Crameri R, Brody AS, Light M, Skov M, Maish W, Mastella G. Allergic bronchopulmonary aspergillosis in cystic fibrosis–state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 2003;37:S225–S264.
2. van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. Thorax 2007;62:276–277.
3. Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. Pediatr Pulmonol 2008;43:607–610.
4. Kanu A, Patel K. Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). Pediatr Pulmonol 2008;43:1249–1251.
5. Lebecque P, Leonard A, Argaz M, Godding V, Pilette C. Omalizumab for exacerbations of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. BMJ Case Rep 2009; 2009:bcr07.2008.0379.
6. Randhawa I, Chin T, Nussbaum E. Resolution of corticosteroid-induced diabetes in allergic bronchopulmonary aspergillosis with omalizumab therapy: a novel approach. J Asthma 2009;46:445–447.
7. Brinkmann F, Schwerk N, Hansen G, Ballmann M. Steroid dependency despite omalizumab treatment of ABPA in cystic fibrosis. Allergy 2010;65:134–135.
8. Elmallah MK, Hendeles L, Hamilton RG, Capen C, Schuler PM. Management of patients with cystic fibrosis and allergic bronchopulmonary aspergillosis using anti-immunoglobulin E therapy (omalizumab). J Pediatr Pharmacol Therap 2012;17:88–92.
9. Wong R, Wong M, Robinson PD, Fitzgerald DA. Omalizumab in the management of steroid dependent allergic bronchopulmonary aspergillosis (ABPA) complicating cystic fibrosis. Paediatr Respir Rev 2013;14:22–24.
10. Lebecque P, Leonard A, Pilette C. Omalizumab for treatment of ABPA exacerbations in CF patients. Pediatr Pulmonol 2009;44:516.
11. Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, Townley R, Casale TB. Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. J Allergy Clin Immunol 2004;113:297–302.
12. Soresi S, Togias A. Mechanisms of action of anti-immunoglobulin E therapy. Allergy Asthma Proc 2006;27:S15–S23.
13. Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, Bao W, Fowler-Taylor A, Matthews J, Busse WW, Holgate ST, Fahy JV. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 2004;170:583–593.