

Case Series of Omalizumab for Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis Patients

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Summary. Allergic bronchopulmonary aspergillosis (ABPA) affects up to 15% of patients with cystic fibrosis (CF). Corticosteroids are used as first-line therapy, but relapse and adverse effects commonly occur. Case reports have suggested the efficacy of the anti-IgE recombinant humanized monoclonal antibody omalizumab. A retrospective multicenter observational French study retrieved 32 CF patients (11 children and 21 adults) who have received omalizumab for more than 3 months in the context of ABPA. Clinical characteristics, concomitant medications (inhaled and oral corticosteroids, antifungal drugs), lung function, body mass index (BMI), and serum IgE were compared at the start and during the first year of omalizumab therapy. Omalizumab-related adverse effects and costs were also evaluated. No significant difference with omalizumab could be demonstrated with regard to lung function, BMI, or the number of patients receiving oral corticosteroids. At the time of initiation of omalizumab, 56% of patients were receiving oral corticosteroids. Five patients were able to discontinue corticosteroids during follow-up and nine patients were able to reduce their daily dose. A total of 78% of the patients had received antifungal therapy at the time of the initiation of omalizumab. Treatment tolerance was good (12.5% of patients experienced side effects). The median cost of omalizumab treatment was €3,620 per

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Conflict of interest: The authors report no conflicts of interest.

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Received 8 June 2016; Revised 5 September 2016; Accepted 19 September 2016.

DOI 10.1002/ppul.23612
Published online in Wiley Online Library
(wileyonlinelibrary.com).

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patient per month. Omalizumab may represent a steroid-sparing therapy in CF patients with ABPA. A randomized-controlled trial is urgently required to provide higher level of evidence regarding the efficacy and cost-effectiveness of omalizumab in CF patients with ABPA. **Pediatr Pulmonol.** © 2016 Wiley Periodicals, Inc.

Key words: cystic fibrosis; allergic bronchopulmonary aspergillosis (ABPA); *Aspergillus fumigatus*; corticosteroids; IgE; immunoglobulin E.

INTRODUCTION

Aspergillus fumigatus is present in the sputum in up to 50% of adults with cystic fibrosis (CF),¹ but allergic bronchopulmonary aspergillosis (ABPA) occurs only in 10–15% of CF patients.² ABPA is associated with accelerated decline in lung function,³ leading to the recommendation of systematic screening, and treatment of ABPA in CF patients.² Pathophysiology of ABPA involves activation of a Th2-mediated adaptive immune response associated with the production of high levels of IgG and IgE against *A. fumigatus*. Because of the allergic nature of the disease, systemic corticosteroids are considered as the first-line therapy for ABPA.² However, patients treated for long periods of time by steroids may experience major adverse effects, raising the interest for steroid-sparing agents. Antifungal oral treatments (e.g., itraconazole and voriconazole) have been proposed in small series of cases as adjunctive therapies in patients with steroid-dependent ABPA or with steroid-related adverse effects.^{4–7} However, no definitive evidence exists regarding their efficacy in the ABPA of CF patient. Antifungal agents should be used with caution, as reports suggested their use was associated with potentially severe adverse effects in up to 33% of patients.^{4,6} Furthermore, azole exposure has been associated with the emergence of azole-resistant *A. fumigatus* isolates,⁸ which raises growing concern about their long-term safety.

Omalizumab is a recombinant humanized monoclonal antibody that targets circulating free IgE and prevents its interaction with the high-affinity IgE receptor at the surface of inflammatory cells (e.g., mast cells and basophils), thereby interrupting the allergic cascade.⁹ Omalizumab is used in patients with severe allergic asthma in whom it allowed improvement in asthma control with a steroid-sparing effect.^{9,10} Based on these results, it has been suggested that omalizumab could be beneficial in patients with ABPA.^{11,12} Since 2007, individual case reports have described the effect of omalizumab in a limited number of CF patients with ABPA: in some cases, there were spectacular clinical and biological improvements,^{13–20} but results did not appear as promising in other cases.^{20–22} An interventional phase 4, randomized placebo-controlled study comparing omalizumab to placebo in CF patients with ABPA was terminated prematurely after inclusion of only 14 patients due to

difficulties in recruitment (http://clinicaltrials.gov/ct2/show/NCT_00787917). Thus, it appears difficult at this stage to draw conclusion on potential effects associated with the use of omalizumab in CF patients with ABPA.

In the present study, we reviewed individual files in 32 CF patients who received omalizumab for ABPA in seven CF centers in France. Our goals were to gain knowledge on current practices, including indications and doses and evaluate potential effectiveness on lung function, steroid use, as well as tolerance and costs associated with omalizumab. We hypothesized that treatment with omalizumab had a steroid-sparing effect and could also avoid steroids initiation in case of contraindication to steroids. The primary outcome was evolution of steroid dose over 1 year and secondary outcomes were evolution of FEV₁ and antibiotic use.

METHODS

Data Collection

This multicenter retrospective observational study was performed in seven French CF centers, representing 1,406 CF patients (23% of the French CF population). Patients who were treated with omalizumab for more than 3 months between 2008 and 2012 were included in the study. The diagnosis of ABPA was based on a combination of clinical and biological symptoms according to the recommendations of the literature: unexplained clinical deterioration and lung function decrease, *Aspergillus* positive serology, elevated total, and specific IgE with or without radiological criteria. Patients were eligible for the study only if they fulfilled classic case or minimal diagnostic criteria according to the CFF consensus criteria. Omalizumab treatment in these patients was started either because of steroid dependence or poor tolerance, either as first-line treatment due to a contraindication to steroid therapy. The time between the start of the ABPA episode and the introduction of omalizumab varied from a few months to several years. Age, gender, and cystic fibrosis transmembrane conductance regulator (*CFTR*) genotype data were collected. Clinical characteristics at the initiation of omalizumab treatment, including body mass index (BMI), forced expiratory volume in 1 sec (FEV₁, % predicted), forced vital capacity (FVC, % predicted), total IgE levels,

bacterial colonization were also collected. Concomitant treatment for ABPA, including oral and inhaled steroids, and oral antifungal agents (itraconazole and voriconazole), were recorded. Number of intravenous antibiotics courses were compared in the year before and the year after initiation of omalizumab.

Characteristics of omalizumab treatment, including dosage and duration of treatment, and the occurrence of adverse effects were analyzed. Cost of omalizumab treatment was calculated on a basis of €441.85 per 150 mg of omalizumab and €2.18 for its administration by a nurse. An outpatient hospital visit (€23) was added to the total cost for each patient to account for the real-life conditions of the first injection.

Statistics

Data are median (min-max) or number (%) unless otherwise stated. Comparisons of respiratory function (FEV₁ and FVC), BMI, total IgE levels 3 and 6 months before and 3, 6, and 12 months after starting omalizumab

treatment, as well as the number of courses of antibiotics over the previous year and following year were performed using Bartlett and ANOVA tests. Data were analyzed for normality using Kolmogorov–Smirnov test. All analyses were performed with the R software.

RESULTS

Patients

Twenty-one patients fulfilled classic case of ABPA according to the CFF consensus and 11 patients fulfilled minimal diagnostic criteria of ABPA. Characteristics of CF patients at the time of initiation of omalizumab for ABPA are provided in Table 1. Among 32 patients (21 adults and 11 children), the median (min-max) age was 23 (11–59) years and 34% of patients were men. The median FEV₁ was 56 (22–116) % predicted. The median weight was 46 (22–82) kg. Median total IgE levels were 1,990 (530–6890) kU/L (n = 27 patients; missing data in 5 patients). However, the five patients without data have

TABLE 1—Characteristics of CF Patients With ABPA (n = 32) at the Time of Omalizumab Initiation

Characteristics	All patients, n = 32	Children, n = 11	Adults, n = 21
Age (years)	23 (11–59)	14 (11–18)	30.5 (19–59)
Gender			
Male	11 (34%)	3 (27%)	8 (38%)
CFTR mutations			
F508del homozygote	17 (53%)	7 (64%)	10 (48%)
F508del composite	13 (41%)	4 (36%)	9 (43%)
Composite	2 (6%)	0	2 (9%)
BMI			19.7 (17.1–29.2)
Z-score BMI		–1.3 (–2.8 to 1)	
Pulmonary function			
FEV ₁ , % pred	56 (22–116)	77 (46–89)	42.5 (22–116)
FVC, % pred	79.5 (43–116)	91 (72–114)	66 (43–116)
Bronchial colonization			
<i>Pseudomonas aeruginosa</i>	21 (65%)	8 (73%)	13 (62%)
<i>Staphylococcus aureus</i>	18 (56%)	5 (45%)	13 (62%)
<i>A. fumigatus</i>	18 (56%)	6 (55%)	12 (57%)
<i>Nontuberculous mycobacteria</i>	2 (6%)	0	2 (9%)
<i>Scedosporium</i>	3 (10%)	1 (9%)	2 (9%)
Serum total IgE kU/L	1990 (419–6890)	1051 (642–5918)	1630 (419–6890)
Corticosteroid therapy			
Oral	18 (56%)	4 (36%)	14 (66%)
Inhaled	24 (75%)	8 (73%)	16 (76%)
Complications	15 (47%)	4 (36%)	11 (52%)
Diabetes			
All	13 (41%)	2 (18%)	11 (52%)
Treated with insulin	11 (34%)	2 (18%)	9 (43%)
Duration of ABPA (months)	3 (0–84)	5 (0–84)	3 (0–72)
Previous episodes of ABPA	21 (65%)	8 (72%)	13 (61%)
Indications of omalizumab			
Steroid side effect	15 (47%)	4 (36%)	11 (52%)
Contraindications to steroids	14 (43%)	7 (63%)	7 (33%)
Insufficient response to steroids	12 (37.5%)	4 (36%)	8 (38%)

Data are median (min-max) or number (%).

CFTR, cystic fibrosis transmembrane conductance regulator; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity.

been previously (within the previous 6 months) tested for total serum IgE which were elevated (>500 or $1,000$ IU/ml) in all patients. Thirteen patients (41%) had diabetes, of whom 85% were insulin-dependent. Fifteen patients (47%) had a history of allergy or atopy and 21 patients (65%) had previously experienced ABPA episodes.

At the time of initiation of omalizumab, 18 patients (56%) were prescribed oral steroids and 24 (75%) were prescribed inhaled steroids. A total of 14 patients (44%) had stopped oral steroids because of adverse effects. Fifteen patients (47%) had experienced at least one complication associated with prolonged use of systemic steroids: diabetes ($n=6$), Cushing's syndrome ($n=6$), osteopenia ($n=4$), osteoporosis ($n=1$), osteochondritis ($n=1$), adrenal insufficiency ($n=1$). Twenty-five patients (78%) had previously taken azole therapy (itraconazole and/or voriconazole) before receiving

omalizumab and eighteen (56%) were still under azole therapy when omalizumab was initiated.

Omalizumab Regimen, Tolerance, and Cost

The median omalizumab initial dosage was 450 (150–1,200) mg per month. Injections were administered every 2 weeks in 23 cases (72%), every 3 weeks in two cases (6%), and on a monthly basis in seven cases (22%).

Only four patients received doses of omalizumab corresponding to doses recommended by the manufacturer for severe asthma (Table 2). Five patients with known IgE levels and body weight received lower doses than those recommended for severe asthma. Eighteen patients had very high IgE levels (range, 1,100–6,890 kU/L) which when combined with their body weight theoretically made them unsuitable for omalizumab therapy; four of these latter patients received the maximum omalizumab dose

TABLE 2—Doses of Omalizumab in 32 CF Patients

Patient	Weight (kg)	Serum total IgE	Recommended doses (mg per month)	Prescribed doses (mg per month)
Children				
4	22	844	Off abacus	150
5	30	642	450	600
6	56	440 ²	600	300
14	28	5,818	Off abacus	600
15	29	NA ¹		150
17	49	4,743	Off abacus	600
18	32	NA ¹		300
19	39	3,562	Off abacus	860
20	44	973	Off abacus	600
21	30	1,675	Off abacus	600
32	55	1,070	Off abacus	1,200
Adults				
1	53	419 ²	450	150
2	47	605	600	300
3	65	2,913	Off abacus	1,200
7	53	420 ²	600	750
8	55	1,250	Off abacus	600
9	43	1,910	Off abacus	750
10	45	600	600	600
11	44	1,176	Off abacus	750
12	64	5,600	Off abacus	1,200
13	29	3,256	Off abacus	750
16	30	1,051	750	450
22	40	2,123	Off abacus	750
23	54	1,360	Off abacus	600
24	63	6,890	Off abacus	600
25	47	533	600	1,200
26	43	5,050	Off abacus	600
27	48	672	600	300
28	38	NA ¹		900
29	53	1,860	Off abacus	1,200
30	53	NA ¹		1,200
31	82	NA ¹		900

Recommended doses: doses recommended by NOVARTIS Inc for the treatment of severe asthma.

¹All five patients who had no serum total IgE levels available at omalizumab initiation had total IgE > 500 kU/L within 6 months before.

²These patients had serum IgE $> 1,000$ kU/L within 6 months before omalizumab initiation.

(1,200 mg/month), whereas the remaining 14 patients received lower doses. Finally the five patients, for whom no IgE data were available for review, received doses between 150 and 1,200 mg per month.

The median (min-max) duration of omalizumab treatment was 18 (3–50) months. Only three patients (0.9%) were treated for less than 6 months (3, 4, and 5 months). At the time of analysis, eleven patients (34%) had been treated for 6 to 12 months and nineteen (59%) patients received omalizumab for more than 12 months. Nineteen patients (59%) were still under omalizumab at the time of data collection. Thirteen patients (41%) had discontinued the treatment, including two who received lung transplantation and one patient who was deceased. Three patients (9%) experienced sufficient clinical improvement to enable them to stop omalizumab after 20–24 months of treatment without clinical relapse after 1 year in one patient and after 3 years in two patients. Seven patients (22%) discontinued the treatment because it was considered ineffective after a median (min-max) period of 6 (3–24) months.

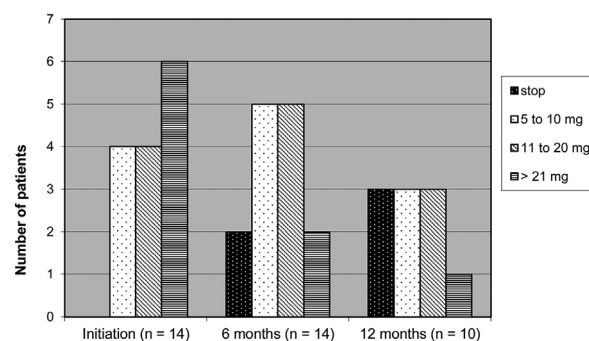
Four patients (12.5%) experienced mild adverse effects, including two cases of mild burns at injection site, a skin eruption coinciding with the injection and one case of tingling and swollen lips.

The median (min-max) direct cost associated with omalizumab treatment was €3,620.36 (€454.18–€7,236.36)/patient/month.

Disease Evolution Under Omalizumab Therapy

Among patients who were prescribed oral steroids ($n = 18$; doses between 10 and 40 mg/day) in conjunction with omalizumab, five (27.5%) patients were able to stop steroids and nine patients (50%) were able to reduce their daily dose between 6 and 12 months after starting omalizumab treatment. In four patients (22%), steroid doses were unchanged during omalizumab therapy (Fig. 1). No significant difference in FEV₁ (% predicted) or in FVC (% predicted) between the start of omalizumab treatment and the year following omalizumab initiation was found ($P = 1$ and $P = 0.93$, respectively) (Table 3). Changes in FEV₁ with omalizumab showed a wide dispersion of values (range –23 to +23%) with a median of 0% (Fig. 2). Only four patients improved their FEV₁ over 10% predicted. For the five patients who were able to stop steroids, changes in FEV₁ varied from +2 to +9% with a median of +4%. Median changes in FEV₁ depending on the age, of steroids or azole treatment are summarized in Table 4. No difference was found in the number of intravenous antibiotic days between the year preceding and the year following the introduction of omalizumab (not shown).

a – Adults (mg/day)



b – Children (mg/kg/day)

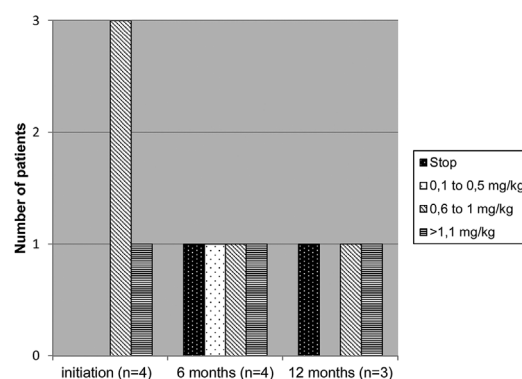


Fig. 1. Doses of corticosteroid at initiation, 6 and 12 months of treatment. At 12 months two patients had discontinued omalizumab before 1 year of treatment.

DISCUSSION

Omalizumab is approved and available for the treatment of severe asthma in France, and the present study revealed that omalizumab was also used off-label in a rather large number of CF patients with ABPA. Omalizumab was usually prescribed with oral steroids and/or oral antifungal agents, although it was sometimes

TABLE 3—Comparison of FEV₁ % Predicted, BMI, and IV Antibiotics Before and After 1 Year of Omalizumab Therapy

	Before omalizumab	After omalizumab	
FEV ₁ % predicted			
All	56 (16–116)	54 (27–124)	$P = 1$
Children	77 (46–89)	70.5 (51–89)	
Adult	41 (26,4–116)	45 (27–104)	
Z-score			
BMI children	–1,3 (–2,8–1)	–1,25 (–2,5–1)	$P = 0,96$
BMI Adult	19,65 (17,5–29,2)	18,9 (16,6–23,4)	$P = 0,97$
Antibiotic IV			
All	2,5 (0–10)	3 (0–10)	$P = 0,95$
Children	3 (1–6)	2,5 (1–7)	$P = 0,95$
Adult	2 (0–10)	3 (0–10)	$P = 0,9$

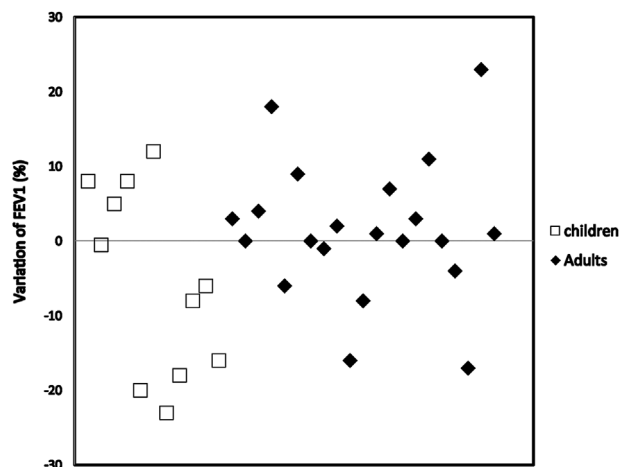


Fig. 2. Variations of FEV₁ (% predicted) for the patients (21 adults and 11 children) between the start of omalizumab treatment and the year following omalizumab initiation.

prescribed as the only ABPA therapy in patients with steroid-related adverse effects or contraindication to steroids. Omalizumab appeared well tolerated in most patients with only minor adverse effects. The majority of patients received lower doses of omalizumab than those recommended for severe asthma. Under omalizumab therapy, steroid doses were tapered in the majority of patients, suggesting a steroid-sparing effect, but most patients were unable to discontinue steroids. High direct costs were associated with omalizumab therapy, suggesting the need for randomized clinical trials of omalizumab in CF patients with ABPA.

The present report describes the largest series of CF patients who received omalizumab for ABPA: a review of the available literature retrieved only 18 cases published from 2007 to 2014.^{13–21} Although, most published cases suggested that omalizumab therapy was associated with major health benefits in CF patients, this conclusion was likely affected by a publication bias. The present study was able to evaluate a rather large number of cases, allowing for description of a broader picture of omalizumab use in the real-life in CF patients with ABPA.

First the present data confirmed that omalizumab was well tolerated in most CF patients, as the most commonly reported adverse effects were pain at the injection site and limited cutaneous rash. These adverse effects did not limit the use of omalizumab that was prematurely discontinued only in one adult patient due to severe headaches and arthralgia. This tolerance profile was reassuring and comparable to what is reported in patients with severe atopic asthma.²³ These findings confirm that omalizumab appears as a safe therapeutic option in pediatric and adult CF patients.

Although, omalizumab is usually prescribed with oral steroids, omalizumab was prescribed without oral steroids in 44% of these CF patients because many patients had previously experienced adverse effects of steroids or had comorbidities (e.g., diabetes and/or osteoporosis) that were considered severe enough to preclude the use of steroids. Among patients taking oral steroids at the start of omalizumab treatment, more than 75% of the patients were able to lower their steroid doses, but less than one third of the patients discontinued steroids in the year following omalizumab initiation. These findings are in marked contrast with previously published reports in which investigators reported that it was possible to discontinue steroids in 15/18 (83%) patients between 6 weeks and 18 months after initiation of omalizumab.^{13–15,17–21} Several reasons may explain this discrepancy. First our population was largely composed of adult patients, whereas previous reports were on pediatric patients with only three cases published in adults. Because CF is a progressive disease, adult patients could be at a more advanced stage of the disease in which steroid discontinuation may be more difficult to achieve. Second, no recommendation exists on the dosage of omalizumab for CF patients with ABPA, resulting in the use of heterogeneous doses (see Table 2). In the published cases, the dose of omalizumab was reported in only 12/18 patients and varied between 300 and 900 mg per month; because data on weight and IgE level were often missing in previous reports, it is unclear whether patients received recommended doses or not. We speculate that the use of low doses of omalizumab could be associated with

TABLE 4—Median Change in FEV₁ After One Year of Omalizumab Therapy

Median change in FEV ₁		Children		Adults	
All patients	n = 11	–6% (–23 to +12)		n = 21	+1% (–16 to +23)
Patients with steroids	n = 5	–5% (–23 to +8)		n = 14	+1% (–6 to +23)
Patients without steroids	n = 6	–6% (–20 to +12)		n = 7	+3.2% (–17 to +16)
Patients with azole therapy	n = 9	–6% (–23 to +12)		n = 7	0 (–16 to +4)
Patients without azole therapy	n = 2	–4.5% (–0.5 to +8)		n = 14	+1% (–17 to +23)

reduced treatment efficacy, but further studies will be necessary to establish the optimal treatment dosage. Despite these limitations, our study concurs with reports suggesting that omalizumab may be used as a steroid-sparing or a steroid-replacing agent in CF patients with ABPA.

The present results found marked FEV₁ variations (either increase or decline) in ABPA patients after initiation of omalizumab. These variations were found in patients under various treatment regimens (i.e., with or without oral steroids and/or azole therapies) and in both pediatric and adult patients. In published cases, spirometric data before and after introducing omalizumab were available for 15 patients^{13–15,18,20,21}; FEV₁ improved significantly (over 20% predicted) in 11 cases (73%). Among the 15 patients who were able to stop steroids in these studies, only 4 patients were treated more than 12 months with an improvement in FEV₁ in two cases only.^{18,19} The other 11^{13–17,20,21} have had a maximum follow up of 9 months (6 weeks to 9 months). These data suggest that FEV₁ variations depend on many factors and that it would be extremely difficult to power a placebo-controlled study of omalizumab using FEV₁ as an outcome.

The present study has several limitations related to its retrospective and uncontrolled design. First prescription of omalizumab was decided by physicians. In the absence of guidelines regarding the use of this treatment in CF patients, indications for prescription, doses, and adjunctive therapies were highly variable among patients. The absence of a placebo group resulted in difficulties in the interpretation of the evolution of patient characteristics and therapies under omalizumab treatment. Despite these limitations, current experience with omalizumab in CF patients with ABPA is extremely limited and these real-life data suggest that omalizumab was associated with a steroid-sparing effect in CF patients with relapsing ABPA and steroid-related adverse effects. However, we cannot exclude that steroids were reduced overtime due to spontaneous improvement of ABPA, independently of omalizumab therapy.

In conclusion, novel therapeutic options are urgently needed for CF patients with ABPA, in whom ABPA treatment often requires long-term steroids with substantial adverse effects. Results of the present study, combined with those of individual case reports available in the literature, suggest that omalizumab could represent an interesting therapeutic option for the treatment of ABPA in CF patients, especially in steroid-dependent patients and in patients with contraindications to steroids. Because observational uncontrolled studies are unlikely to provide definitive evidence on the effect of omalizumab in CF patients with ABPA and because omalizumab is associated with high treatment costs, we suggest that obtaining data

from a placebo-controlled study evaluating the steroid-sparing effect and cost-effectiveness of omalizumab in CF patients with ABPA is urgently needed.²⁴ Additionally, studies assessing the efficacy of omalizumab in paediatric CF patients should include appropriate age-specific endpoint (e.g., growth). Until these studies have been performed, no definitive conclusion can be drawn regarding potential benefits associated with omalizumab in CF children and adults with ABPA.

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