Annals of Pharmacotherapy
1–6

DOI: 10.1177/1060028015624204
aop.sagepub.com
SAGE

Omalizumab Treatment for Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

Nagehan Emiralioglu, MD[1], Deniz Dogru, MD[1], Gokcen Dilsa Tugcu, MD[1], Ebru Yalcin, MD[1], Nural Kiper, MD[1], and Ugur Ozcelik, MD[1]

Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF) is characterized by destructive changes in the airways. Long-term treatment with oral corticosteroids is often required for repeated exacerbations. Because elevated total IgE is a cardinal abnormality of ABPA, omalizumab has been used sporadically to decrease corticosteroid dose or totally replace corticosteroids. **Objective:** The aim of this report is to describe our experience with omalizumab treatment in patients with CF and ABPA. **Methods:** We conducted a review of 6 CF patients with ABPA receiving omalizumab. All patients were treated with oral prednisolone and itraconazole. Omalizumab was started if the patient was not responding to steroid treatment, which was determined according to serum IgE levels and/or clinical findings or depending on if there were side effects caused by steroid treatment. **Results:** The mean age of patients at the beginning of omalizumab treatment was 16.1 years. One patient had a new diagnosis of ABPA; however, the others had the first to third exacerbation when treated with omalizumab. The mean duration of ABPA by the time that treatment with omalizumab started was 13 ± 12.4 months (range = 2-29 months). With omalizumab treatment, IgE levels were decreased in all patients, and *Aspergillus*-specific IgE levels were decreased in 4 patients; however, FEV_1 (% predicted) improved only in 2 patients who had mild disease. Corticosteroids were reduced in the first, second, and third months of omalizumab treatment in 2, 1, and 3 patients, respectively. In 2 patients, steroid treatment was stopped. None of the patients suffered from side effects of omalizumab. The mean duration of omalizumab treatment was 12.5 months (range = 6-18 months). **Conclusions:** This study showed steroid-sparing effect, decreasing IgE levels, and improvement in respiratory symptoms in 6 CF patients with omalizumab treatment. Although this is a small sample of the population, omalizumab may be an alternative therapy for ABPA in CF patients who fail to respond to systemic corticosteroids or have serious adverse effects.

Keywords

ABPA, *Aspergillus*, cystic fibrosis, omalizumab

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary hypersensitivity disorder usually induced by *Aspergillus fumigatus*. It is a noninvasive inflammatory lung disease found in immunocompetent individuals, typically with a diagnosis of asthma or cystic fibrosis (CF).[1] ABPA occurs in 2% to 25% of patients with CF and causes progressive deterioration of lung function and increased respiratory symptoms.[2,3]

Although the pathogenesis of ABPA has not been clearly understood yet; patients with ABPA have enhanced Th2 cell response to *A fumigatus*, increased specific IgE production against *A. fumigatus*, and raised total serum IgE.[4] The diagnosis of ABPA in CF is based on the presence of a combination of clinical, laboratory, and radiological findings.[2]

The main aim of treatment in ABPA is to reduce episodic acute inflammation, therefore limiting disease progression with resultant airway destruction.[1] Systemic corticosteroids are the mainstay of therapy for treatment of acute exacerbations and to prevent progressive lung damage in combination with antifungals (eg, itraconazole) to decrease the fungal antigen burden.[5] However, these treatments are often insufficient to control symptoms or lead to intolerable side effects; as a result, alternative therapies have been investigated.[6]

Omalizumab is a humanized monoclonal antibody to IgE targeting the high-affinity Fc receptor of IgE and has

[1]Hacettepe University Faculty of Medicine, Department of Pediatric Pulmonology, Ankara, Turkey

Corresponding Author:
Nagehan Emiralioğlu, Hacettepe University Faculty of Medicine, Ihsan Dogramaci Children's Hospital, Sıhhiye, Ankara, Turkey.
Email: drnagehan@yahoo.com

been used sporadically in an effort to decrease corticosteroid dose because of the steroid-sparing effect.[6] There have been conflicting case reports in the literature about the long-term success of omalizumab, and there have been no randomized clinical trials of omalizumab. Existing case reports mainly showed good clinical responses with rapid and good improvement of respiratory symptoms and lung function and successful cessation of corticosteroids in the treatment of ABPA in CF with omalizumab. However, omalizumab failed in a CF patient with ABPA for 4 years when treatment was started. The patient experienced a severe relapse with FEV1 decline and remained steroid dependent over the treatment period.[7] The aim of this report is to describe our experience with omalizumab treatment in patients with CF and ABPA.

Methods

We conducted a retrospective review of CF patients with ABPA receiving omalizumab treatment from October 2013 to July 2015. Informed consent was taken from the parents for omalizumab treatment. Approval of ministry of health was obtained before the omalizumab treatment for each patient.

Diagnosis of CF in all patients was based on typical clinical presentation together with at least 2 positive sweat chloride tests and/or 2 CF-causing CFTR mutations.[8] ABPA diagnosis was based on the criteria published in the ABPA consensus paper, that included 5 or more of the following: (*a*) acute or subacute clinical deterioration not attributable to another etiology; (*b*) total serum IgE concentration higher than 500 IU/mL; (*c*) immediate cutaneous reactivity to *Aspergillus*; (*d*) presence of serum IgE antibodies to *A. fumigatus*; (*e*) precipitins or IgG antibodies to *A. fumigatus*; (*f*) new or recent pulmonary infiltrates, mucus plugging, or bronchiectasis that have not cleared with antibiotics and physiotherapy.[2] Patients who were diagnosed with ABPA were treated with oral prednisolone 1 to 2 mg/kg/day and itraconazole 5 mg/kg/day. Prednisolone dose was tapered by 0.25 mg/kg according to serum IgE levels, which were checked every 1 to 2 months.

Patients were diagnosed as having "exacerbation of ABPA" if total serum IgE concentration was higher than 500 IU/mL or there was a >2-fold rise from baseline, results of serology for ABPA (*Aspergillus* precipitins or *Aspergillus*-specific IgE or IgG) were positive, there were new infiltrates on chest radiography or chest CT, and there was worsening pulmonary function or pulmonary symptoms.[2] In such a case, ABPA treatment, including steroids (1-2 mg/kg/day) with itraconazole, was started again if it had already been stopped or the dose of steroid was increased up to 1 to 2 mg/kg if the patient was already on steroids. If CF-related infection was suspected at the same time, concomitant antibiotics were also added.

Omalizumab was started if the patient was not responding to steroid treatment, which was determined according to serum IgE levels and/or clinical findings, or if there were side effects of steroid treatment. These side effects were diabetes mellitus in 4 patients and Cushing syndrome in 2 patients. The response to steroids was assessed according to clinical and radiological findings, decline in FEV_1(% predicted), and increase in IgE and *Aspergillus*-specific IgE levels under treatment. Symptoms were evaluated using medical history, which was recorded in the patient's chart. In this chart, we queried for information on the characteristics of cough, sputum, dyspnea, fever, and history of antibiotic use. Omalizumab (300 mg dosage) was administered subcutaneously every 4 weeks. Dosage was individually adapted to body weight and IgE level at the beginning of treatment referring to the prescribing recommendation of omalizumab for allergic asthma.[9] While receiving omalizumab treatment, all patients continued itraconazole treatment and their routine medication for CF.

Patients' respiratory symptoms (cough, sputum, and dyspnea in medical history), acute pulmonary exacerbations, serum IgE and *Aspergillus*-specific IgE levels, spirometry findings, and corticosteroid dosage were recorded at each monthly visit.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 20.0. Continuous variables were presented as a mean ± SD for normal distributions or median (min-max) for nonnormal distributions. Wilcoxon's rank-sum test was used to compare continuous variables between 2 dependent groups. A P value of 0.05 (2-sided) was considered statistically significant.

Results

A total of 28 CF patients were diagnosed with ABPA and were treated with oral corticosteroids and itraconazole in our department between 2013 and 2015. Among these 28 patients, a total of 6 patients received omalizumab. Two of them received omalizumab because they were not responding to steroid treatment, and 4 patients received omalizumab because they had diabetes mellitus with steroid treatment.

There were 2 male and 4 female patients. The mean age of patients at the beginning of omalizumab treatment was 16.1 years (±7.9, range = 11-32 years). The mean age of the first ABPA diagnosis was 12.9 years (±8.02, range = 5-28 years). All the patients had increased cough and sputum and decline in FEV_1(% predicted) before the therapy. The clinical and laboratory characteristics of the patients prior to therapy are shown in Table 1. One patient had the new diagnosis of ABPA; however, the others had the first to third exacerbation of ABPA when treated with omalizumab. The

Table 1. Clinical Characteristics of Patients.

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Female	Female	Female	Male	Female	Male
Mutation	G542X+/−	ΔF508+/+	ΔF508+/−	ΔF508+/+	3120+1GA+/+	ΔF508+/−
Chronic colonization with *Pseudomonas aeruginosa*	Positive	Negative	Negative	Positive	Positive	Positive
Aspergillus in sputum in the beginning of omalizumab	Negative	Positive	Positive	Negative	Positive	Positive
Age at diagnosis with CF	1 month	6 months	15 years	1 month	3 months	11 months
Age at first ABPA diagnosis	13 years	12 years	28 years	5 years	8 years	10 years
Age at the beginning of omalizumab treatment	14 years	16 years	32 years	11 years	11 years	13 years
Duration of ABPA before omalizumab treatment	2 months	19 months	29 months	2 months	24 months	2 months
Number of ABPA exacerbations before omalizumab treatment	No	2	1	3	1	1
Total steroid duration before omalizumab treatment	2 months	19 months	29 months	2 months	24 months	2 months
Reason for omalizumab treatment	Adverse effect of steroid (diabetes mellitus)	Adverse effect of steroid (diabetes mellitus)	No response to steroid	Adverse effect of steroid (diabetes mellitus, Cushing syndrome)	No response to steroid	Adverse effect of steroid (diabetes mellitus, Cushing syndrome)

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis.

mean duration of ABPA by the time treatment with omalizumab started was 13 ± 12.4 months (range = 2-29 months).

At the beginning of treatment with omalizumab, the mean FEV_1% predicted of all patients was 57.8% (range = 35%-89%, ±19.6%). Although there were improvements in lung function tests in 2 patients (case 1 and case 6), at the end of the treatment, the mean FEV_1% predicted was 60.8% (range = 30%-86%, ±27.2%). There was no significant difference in mean FEV_1% predicted after the treatment(P=0.91).FEV_1% predicted improved in the patients with high initial FEV_1% predicted because of mild disease, although FEV_1% predicted did not change in the patients with severe disease (Table 2). Also, omalizumab treatment was related to significant reduction in IgE (P = 0.028). Before the treatment with omalizumab, the mean total IgE was 698 ± 67.52 IU/mL (range = 609-800 IU/mL); after the treatment it was 391 ± 125.54 IU/mL (range = 279-629 IU/mL). Four of the patients also had decreased *Aspergillus*-specific IgE levels after omalizumab treatment (P = 0.062).

Corticosteroids were reduced in the first, second, and third months of omalizumab treatment in 2, 1, and 3 patients, respectively. In 2 patients, steroid treatment has been stopped (Table 2); 4 of the patients had no pulmonary exacerbation during the omalizumab therapy, 1 of the patients died as a result of respiratory failure (case 5), and the other patient had pulmonary exacerbation during the treatment and did not want to continue the treatment anymore (case 2). Clinical and laboratory findings after the treatment with omalizumab are shown in Table 2, and changes in FEV_1% predicted and IgE levels during omalizumab treatment are shown in Figure 1.

The mean duration of omalizumab treatment was 12.5 months (±5.4, range = 6-18 months). Four of the patients had no pulmonary exacerbation caused by CF-related infection or worsening symptoms noted in their medical history while receiving omalizumab treatment and decreasing steroid therapy, as shown in Table 2. Also none of the patients had exacerbation of ABPA during omalizumab treatment. During clinical follow-up, none of the patients suffered from side effects of omalizumab.

Discussion

ABPA is characterized by a variety of clinical and immunological responses to antigens of *A. fumigates*, and untreated disease for prolonged periods of time can result in irreversible lung damage.[3] Therefore, early detection and treatment of ABPA is critical in preventing serious pulmonary damage such as bronchiectasis. Corticosteroids are the mainstay of treatment for ABPA, targeting the inflammatory response triggered by *A. fumigatus*. Also, antifungals have an adjunctive role in the treatment of ABPA by decreasing the burden of fungal organisms and antigenic stimulation.[4] However,

Table 2. Clinical and Laboratory Findings Before and After Treatment With Omalizumab.

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Initial FEV1% predicted	67	50	35	89	42	64
FEV1% predicted after omalizumab treatment	86	48	30	84	32	85
Initial IgE (IU/mL)	726	646	609	725	682	800
IgE after omalizumab treatment (IU/mL)	298	279	371	400	369	629
Aspergillus-specific IgE before omalizumab treatment (kU/L)	24.7, Class 4	48.2, Class 4	13.2, Class 3	14.9, Class 3	13.6, Class 3	5.05, Class 3
Aspergillus-specific IgE after omalizumab treatment (kU/L)	0.12, Class 0	NA	0.08, Class 0	5.41, Class 3	NA	0.14, Class 0
Steroid dosage reduction time after omalizumab treatment (month)	1 month	1 month	3 months	2 months	3 months	3 months
Steroid treatment	Stopped after 15 months of omalizumab	Still being continued	Still being continued	Stopped after 6 months of omalizumab	Died	Still being continued
Number of acute pulmonary exacerbations caused by CF-related infection during omalizumab treatment	None	1	None	None	2	None
Course of disease	Alive	Alive	Alive	Alive	Died (respiratory failure)	Alive
Duration of treatment with omalizumab (months)	18	6	16	18	9	8
Course of omalizumab	Still being continued	Stopped (patient did not want to continue)	Still being continued	Still being continued	Died	Still being continued

Abbreviations: CF, cystic fibrosis; NA, not available.

prolonged oral steroid therapy is especially problematic for patients with CF, who are already predisposed to diabetes, osteopenia, and growth retardation.[10]

Omalizumab, a monoclonal antibody against IgE, should be considered in CF patients with ABPA who are unresponsive to conventional therapy or require prolonged use of oral steroids.[11] Omalizumab has been approved for use in patients older than 12 years with moderate to severe allergic asthma, and it is being more widely used for CF and ABPA. However, there is no completed randomized, double-blind, and controlled multicenter trial with omalizumab in CF patients. Several case reports and small series have suggested its potential effect in CF patients with ABPA.[12-15]

Omalizumab downregulates IgE receptors and decreases free IgE concentrations, but anti–IgE-IgE complexes may result in increase of total IgE.[16] Because of this, measuring total IgE is impractical for assessing ABPA treatment response to omalizumab.[17] In this report, the significance of the observed decrease in serum IgE is unclear. Wong et al[15] also reported clear reductions in IgE with omalizumab in their 2 cases. Serum IgE is often used as a marker of disease exacerbation in ABPA. It is unknown whether the reduction in total serum IgE is part of the natural course of ABPA or a successful treatment with omalizumab. However, measuring free IgE provides good information to assess the response to omalizumab.[17] Four of the patients had decreased free IgE levels, which corresponded to their overall clinical improvement. Recent case reports have also shown a relationship between decreased free IgE levels and improvement in the clinical condition of ABPA patients with CF.[13,14]

In previous studies, anti-IgE treatment is related to a significant increase in FEV_1, reduced frequency of respiratory symptoms, and decreased use of corticosteroids.[6,18] Despite the improvement in FEV_1% predicted in 2 of our patients, we did not find a significant difference in lung function tests. This may be related to the wide age range (11 years to 32 years) of these 6 patients. The oldest patient had the worst lung function results and did not improve with omalizumab. However, 4 of the patients had no pulmonary exacerbation during omalizumab treatment, and respiratory symptoms decreased. Pulmonary exacerbations also contribute to deterioration in lung function, which could be the reason for a decline in FEV_1%. In this study, we noticed that

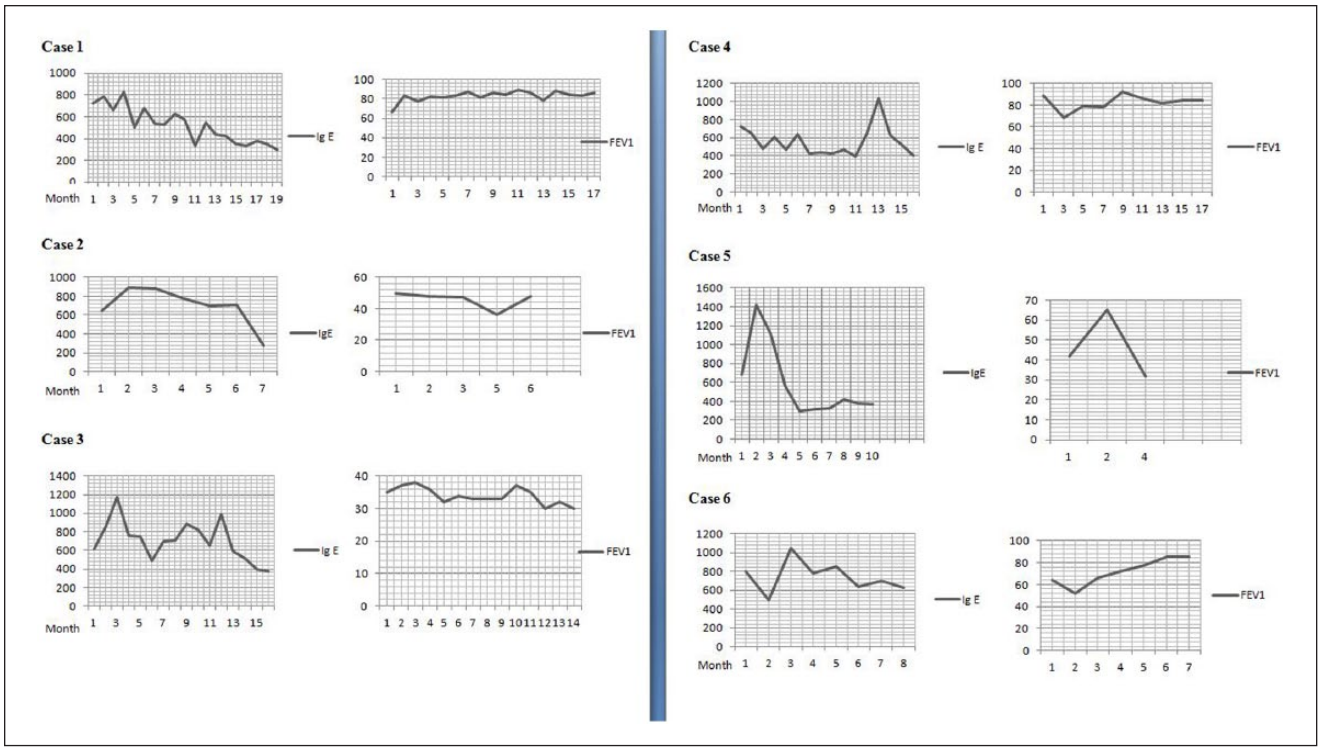

Figure 1. Change in FEV1% predicted and IgE levels (IU/mL) of each patient during omalizumab treatment.

patients with an early introduction of omalizumab showed a good response, but with regard to long-term diagnosis of ABPA and long-term use of corticosteroids, we observed that the clinical response was limited. Furthermore, deterioration in lung function continued in patients with low FEV_1%, even though they had been receiving the omalizumab treatment. Considering the results for these 6 patients, we recommend that omalizumab should be started before clinical deterioration and severe decline in lung function tests.

Steroid-sparing effects of omalizumab have been previously reported in patients with ABPA and allergic asthma, but conflicting reports exist in CF.[19] As in our cases, successful weaning within 1 to 3 months of omalizumab treatment have been reported.[12] Our results in these 6 patients indicate that omalizumab treatment may offer a corticosteroid-sparing treatment option and improvement in respiratory symptoms. Although anaphylaxis has been noted as an adverse effect with omalizumab, the 6 CF patients in our study did not experience any such side effect.

This was a retrospective study showing the steroid-sparing effect, decrease in IgE levels, and improvement in respiratory symptoms in patients with CF and ABPA during omalizumab treatment. But we could not measure the free IgE levels, which is a valuable assessment of response to omalizumab. Also, the small number of patients in this retrospective review precludes definitive statements regarding the effectiveness and safety of omalizumab as an alternative treatment modality in CF patients with ABPA. Meanwhile, early treatment benefits patients in a stable condition, leading to lower doses or absence of systemic steroid use. However, there is a need for large prospective randomized controlled trials of omalizumab therapy in CF patients with ABPA, with evaluation of both clinical and laboratory outcome measures such as steroid requirement, ABPA exacerbations, and lung function.

Conclusions

In conclusion, prolonged use of prednisolone therapy for ABPA may result in glucose intolerance, decreased bone density, and linear growth retardation, for which CF patients are at increased risk. In our retrospective analysis with 6 patients, we showed the steroid-sparing effect, decrease in IgE levels, and improvement in respiratory symptoms with omalizumab treatment. Although this is a small sample with a wide age range, we believe that early initiation of omalizumab may be an alternative therapy in CF patients with prior adverse prednisolone effects or who fail to respond to systemic corticosteroids.

Authors' Note

Dr Nagehan Emiralioglu collected data, searched the literature, analyzed the data, and prepared the draft of the article. Dr Deniz Dogru

took part in the project design and literature research and revised the manuscript critically for important intellectual content. Dr Gokcen Dilsa Tugcu took part in data collection and interpretation of data. Dr Ebru Yalcin took part in analysis of data and review of the manuscript. Dr Nural Kiper took part in the review of the manuscript and approval of the version to be published. Dr Ugur Ozcelik took part in study design and review of manuscript; she agreed to be accountable and willing to investigate and resolve all questions pertaining to accuracy and integrity of the work. This study was performed in Hacettepe University Faculty of Medicine Ihsan Dogramaci Children's Hospital in Ankara, Turkey. Dr Nagehan Emiralioglu presented this data at the 38th ECFS Conference in Brussels, June 10-13, 2015.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Hogan C, Denning DW. Allergic bronchopulmonary aspergillosis and related allergic syndromes. *Semin Respir Crit Care Med*. 2011;32:682-692.
2. Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis*. 2003;37:225-264.
3. Maturu VN, Agarwal R. Prevalence of *Aspergillus* sensitization and allergic bronchopulmonary aspergillosis in cystic fibrosis: systematic review and meta-analysis. *Clin Exp Allergy*. 2015;45:1765-1778.
4. Mahdavinia M, Grammer LC. Management of allergic bronchopulmonary aspergillosis: a review and update. *Ther Adv Respir Dis*. 2012;6:173-187.
5. Judson MA, Stevens DA. Current pharmacotherapy of allergic bronchopulmonary aspergillosis. *Expert Opin Pharmacother*. 2001;2:1065-1071.
6. Tanou K, Zintzaras E, Kaditis AG. Omalizumab therapy for allergic bronchopulmonary aspergillosis in children with cystic fibrosis: a synthesis of published evidence. *Pediatr Pulmonol*. 2014;49:503-507.
7. Jat KR, Walia DK, Khairwa A. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2015;(11):CD010288.8.
8. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr*. 1998;132:589-595.
9. Omalizumab (Xolair®) full prescribing information (EU). http://www.gene.com/download/pdf/xolair_prescribing.pdf
10. Cohen-Cymberknoh M, Blau H, Shoseyov D, et al. Intravenous monthly pulse methylprednisolone treatment for ABPA in patients with cystic fibrosis. *J Cyst Fibros*. 2009;8:253-257.
11. 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 Ther*. 2012;17:88-92.
12. Van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax*. 2007;62:276-277.
13. Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. *Pediatr Pulmonol*. 2008;43:607-610.
14. Kanu A, Patel K. Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). *Pediatr Pulmonol*. 2008;43:1249-1251.
15. 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.
16. Nowak D. Management of asthma with anti-immunoglobulin E: a review of clinical trials of omalizumab. *Respir Med*. 2006;100:1907-1917.
17. Belliveau PP. Omalizumab: a monoclonal anti-IgE antibody. *Medscape Gen Med*. 2005;7:27.
18. 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:pii:bcr07.2008.0379.
19. Sastre I, Blanco J, Mata H, Garcia F. A case of allergic bronchopulmonary aspergillosis treated with omalizumab. *J Investig Allergol Clin Immunol*. 2012;22:145-147.