

Allergic Bronchopulmonary Aspergillosis Treated with Mepolizumab and Omalizumab: Switching Biological Agents

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ABSTRACT

Objective: Allergic bronchopulmonary aspergillosis (ABPA) is a fungal infection commonly seen in patients with uncontrolled severe asthma. Standard treatment includes glucocorticoids and itraconazole; however, the use of biological agents such as omalizumab and mepolizumab has shown promise in patients unresponsive to conventional therapy. This study aims to share the clinical characteristics of ABPA patients who were uncontrolled with glucocorticoids and itraconazole and subsequently treated with mepolizumab or omalizumab.

Materials and Methods: Eight ABPA patients were included in this retrospective study. The diagnosis was made based on the criteria set by the International Society for Human and Animal Mycology (ISHAM). Clinical features, eosinophil levels, pulmonary function test results, disease stage, and treatment regimens were evaluated.

Results: Among the eight ABPA patients, three were female (37.5%) and five were male (62.5%). The mean age was 51.62 years (± 8.73) with a range of 41 to 62 years. The average serum total IgE level at diagnosis was 1726 (± 516) KU/L. All patients exhibited central bronchiectasis, and the serum eosinophil count ranged from 300 to 1670 cells/ μ L. Seven patients were positive for *Aspergillus*-specific IgE, while one patient tested negative for specific IgE but positive for IgG. Disease staging revealed that 62.5% were in stage 4, 25% were in stage 5b, and 12.5% were in the acute attack stage. All patients received high-dose inhaled corticosteroids, long-acting beta 2 agonists, and leukotriene receptor antagonists. Glucocorticoids and antifungal therapy were initiated in all patients, and omalizumab or mepolizumab was added to the treatment regimen due to drug side effects or inadequate asthma control. All patients initially received omalizumab, but four patients switched to mepolizumab later due to suboptimal asthma symptom control and exacerbations.

Conclusion: The standard treatment for ABPA involves glucocorticoids and itraconazole. However, when glucocorticoids cannot be discontinued or their side effects become problematic, monoclonal antibodies such as omalizumab or mepolizumab can be considered as alternative treatments.

Keywords: Anti-IL-5, allergic bronchopulmonary aspergillosis, biologicals, mepolizumab, omalizumab

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a fungal infection observed in patients with uncontrolled severe asthma. Initially, *Aspergillus fumigatus* settles in the airways, and the spores can persist in the tracheobronchial tree. Hyphae can grow and release antigens and exoproteases. In patients with impaired mucociliary clearance,

eosinophilic inflammation and subsequent hypersensitivity reactions occur. ABPA manifests as difficult-to-treat asthma, eosinophilia in the blood, lungs, and airways, recurrent pulmonary opacities, bronchiectasis, and elevated serum immunoglobulin (IgE) levels (1). ABPA patients may exhibit *Aspergillus fumigatus*-specific IgE through skin prick tests or serum levels. Consolidation, mucoid impaction, and bronchiectasis can be observed on com-

puted tomography. ABPA patients are treated with corticosteroids and itraconazole (2). Glucocorticoids and antifungals may not provide clinical improvement in some patients and can have potential side effects. Additionally, in recent years, biologic drugs such as Omalizumab and Mepolizumab have been used for patients who do not respond successfully to standard treatment (3-5). Omalizumab is a humanized monoclonal antibody that binds to immunoglobulin (IgE) and is effective in patients with severe allergic asthma. It has been shown to reduce asthma symptoms and improve pulmonary function parameters in ABPA patients (3). Mepolizumab is a monoclonal antibody against Interleukin-5 (IL-5) and inhibits eosinophilic activation by blocking IL-5 binding to its receptor. While it is anticipated to be effective in the treatment of ABPA accompanied by eosinophilia, there are only case reports available on this topic (5-7). The comparison of these two biologic agents in ABPA is still limited. In this article, we share long-term follow-up data of ABPA patients transitioning from omalizumab to mepolizumab or receiving omalizumab alone.

MATERIALS and METHODS

Data Collection: This retrospective study included 8 patients diagnosed with ABPA who were treated with either mepolizumab or omalizumab between January 2015 and June 2022. Demographic data, laboratory characteristics, radiological data, and treatment follow-up processes were recorded. The diagnosis of ABPA was evaluated based on the diagnostic criteria set forth by ISHAM (The International Society for Human and Animal Mycology) (2). The use of biological agents was examined in patients who were treated for asthma and ABPA.

The primary aim of this study is to describe the demographic, laboratory, and pulmonary function test characteristics of our ABPA patients. The secondary aim is to investigate the use of biological agents in the treatment of ABPA. Parameters such as age, gender, duration of asthma and ABPA, pulmonary function tests, and disease stage were assessed. Each patient was individually evaluated according to the ISHAM diagnostic criteria.

Details of omalizumab and mepolizumab treatment, including dosage, treatment duration, and adverse effects, were analyzed. Omalizumab treatment was administered based on weight and total IgE levels. If the total IgE level exceeded 1500 (KU/L), an application was made to the Ministry of Health, and omalizumab was administered at

a dosage of 375 mg every 14 days. Mepolizumab treatment was given subcutaneously at a dosage of 100 mg every 4 weeks (8). Similar criteria to the OSMO study were utilized for selecting patients to switch from omalizumab to mepolizumab (9). Non-response to omalizumab treatment was defined as the use of steroids for more than two asthma attacks per year or hospitalization due to one or more asthma attacks per year.

Ethics committee approval was obtained from the University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital for this study (dated 08.09.2022, protocol code: 116.2017.R-252). All patients are currently under follow-up at our clinic, and informed consent was obtained from each participant. Statistical analysis of the study data was performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics such as mean, standard deviation, minimum, and maximum values were reported numerically.

RESULTS

A total of eight patients with severe allergic asthma and allergic bronchopulmonary aspergillosis were included in this study. Among the patients, 3 (37.5%) were female and 5 (62.5%) were male. The mean age of the patients was 51.62 (± 8.73) years, ranging from 41 to 62 years. The diagnosis of allergic bronchopulmonary aspergillosis was based on the ISHAM diagnostic criteria, and all patients met these criteria.

At the time of diagnosis, the serum total IgE levels of the patients with allergic bronchopulmonary aspergillosis were 1726 (± 516) KU/L, ranging from 1025 to 2500 KU/L. All patients exhibited central bronchiectasis. The serum absolute eosinophil count was 1158 (± 542) cells/ μ L, ranging from 300 to 1670 cells/ μ L, and the percentage of eosinophils was 10.6 (± 3.7)%, ranging from 4% to 15%. Seven out of eight patients tested positive for *Aspergillus*-specific IgE, while one patient was negative for specific IgE but positive for IgG. All patients had positive skin prick test results.

The initial pulmonary function test results showed that the forced expiratory volume in 1 second (FEV1) was 47% (± 23), ranging from 20% to 89% predicted. The absolute value of FEV1 was 1716 (± 882) mL, ranging from 540 to 2840 mL. The forced vital capacity (FVC) was 64% (± 16), ranging from 34% to 79% predicted, with an absolute value of 2468 (± 1137) mL, ranging from 990 to 4010 mL.

The FEV1/FVC ratio was 64 (\pm 16), ranging from 34 to 79. Table I presents a summary of the results.

We diagnosed all of our patients according to the International Society for Human and Animal Mycology (ISHAM) Working Group's criteria, which include the following parameters for the diagnosis of bronchial asthma:

1. Elevated specific IgE antibody to *Aspergillus fumigatus* in serum or positive *Aspergillus* skin prick test.
2. Elevated serum eosinophil count (>500 cells/ μ L).
3. Radiological pulmonary opacities.
4. Central bronchiectasis.
5. Mucoïd impaction.
6. Elevated serum total IgE level (>1000 IU/L).
7. Elevated specific IgG antibody to *Aspergillus fumigatus* in serum (2).

All of our patients were treated with a combination of ICS (inhaled corticosteroids) + LABA (long-acting beta-2 agonists) and LTRA (leukotriene receptor antagonist) for their allergic bronchopulmonary aspergillosis (ABPA). We can see all of them in Table II.

When we looked at the disease stages of our patients, 62.5% (n=5) were in stage 4, 25% (n=2) were in stage 5b, and 12.5% (n=1) were grouped as stage 3. ABPA recurrence was not observed in 5 (62.5%) patients who were using the biological agent. 2 mg methylprednisolone treatment is still ongoing in 2 (25%) patients; 1 (12.5%) patient had an attack while under the biologic agent; 1 (12.5%) patient had two attacks while under the biologic agent. Detailed information on disease stages and treatments can be found in Table III.

Changes in asthma control test, eosinophil values, and FEV1 values of patients who were switched to mepolizumab treatment due to inadequate asthma control while receiving omalizumab treatment are detailed in Table IV.

DISCUSSION

Our study provides detailed characteristics of ABPA patients and highlights the use of biological agents, specifically switching from omalizumab to mepolizumab. This is the first study in our country to explore the use of two biological agents in ABPA patients.

The median age of our patients was 51 years, which aligns with previously reported data (10,11), but it is older than in Indian studies (12). Our hospital is a tertiary-level

Table I: Demographic, Laboratory, and Pulmonary Function Test Parameters of the Patients.

Parameter	Average (Standard Deviation)	Minimum - Maximum
Age (years)	51.62 (\pm 8.73)	41 - 62
Gender		
Female	3 (37.5%)	
Male	5 (62.5%)	
Asthma Disease Year	20.5 (\pm 9)	11 - 40
ABPA Disease Year	6.1 (\pm 2.4)	1 - 9
Central Bronchiectasis	8/8 (100%)	
Total IgE Level in Diagnosis of ABPA (KU/L)	1726 (\pm 516)	1025 - 2500
Absolute Eosinophil Count in Diagnosis of ABPA	1158 (\pm 542)	300 - 1670
Percentage of Eosinophils in Diagnosis of ABPA	10.6 (\pm 3.7)	4 - 15
Initial FEV1 in Diagnosis of ABPA (ml)	1716 (\pm 882)	540 - 2840
FEV1 Percentage in Diagnosis of ABPA	47 (\pm 23)	20 - 89
Initial FVC in Diagnosis of ABPA (ml)	2468 (\pm 1137)	990 - 4010
FVC Percentage in Diagnosis of ABPA	59 (\pm 22)	32 - 100
FEV1/FVC	64 (\pm 16)	34 - 79

ABPA: Allergic bronchopulmonary aspergillosis, **IgE:** Immunoglobulin E, **KU/L:** Kilounits per liter, **ml:** Milliliters.

Table II: International Society for Human and Animal Mycology (ISHAM) Working Group's criteria of our patients.

	Asthma	Specific IgE to Aspergillus Fumigatus	Skin Prick Test to Aspergillus	Serum Eosinophil Count	Serum IgE Level	Precipitin IgG to Aspergillus Fumigatus	Central Bronchiectasis/ Mucoïd Impaction	ICS+ LABA+ LTA
Case 1	Yes	Positive	Positive	730	1278	Negative	Yes	Yes
Case 2	Yes	Positive	Positive	570	1500	Negative	Yes	Yes
Case 3	Yes	Positive	Positive	1600	1025	Negative	Yes	Yes
Case 4	Yes	Positive	Positive	1400	1340	Negative	Yes	Yes
Case 5	Yes	Negative	Positive	1350	1980	Positive	Yes	Yes
Case 6	Yes	Positive	Positive	1650	2500	Negative	Yes	Yes
Case 7	Yes	Positive	Positive	1670	2230	Negative	Yes	Yes
Case 8	Yes	Positive	Positive	300	1960	Negative	Yes	Yes

Table III: Disease stages and treatment details.

	ISHAM Stage	Initial Treatment	Steroid Side Effect and Treatment Response	First Biological Agent	Total follow-up period after omalizumab	Clinically	Total follow up period after mepolizumab
Case 1	Stage 4	Itraconazole + methylprednisolone	Blood sugar regulation was impaired due to diabetes.	Omalizumab	36 months	Recurrence, asthma attacks	12 months
Case 2	Stage 4		Osteoporosis, Steroid dose could not be reduced	Omalizumab	12 months	Asthma control could not be achieved	12 months
Case 3	Stage 5b		Steroid dose could not be reduced	Omalizumab	42 months	There were two ABPA exacerbations in the follow-up, still taking 2mg of methylprednisolone tablets daily.	-----
Case 4	Stage 4		Asthma control could not be achieved	Omalizumab	64 months	There was one ABPA exacerbations in the follow-up. Improved	-----
Case 5	Stage 5b		Blood sugar regulation was impaired due to diabetes. Myopathy developed.	Omalizumab	24 months	When methylprednisolone was stopped; symptoms, IgE increased, and PFT parameters decreased. still taking 2 mg of methylprednisolone tablets daily.	-----
Case 6	Stage 3		Blood sugar regulation was impaired due to diabetes.	Omalizumab	36 months	Exacerbation.	-----
Case 7	Stage 4		Asthma control could not be achieved	Omalizumab	12 months	Asthma control could not be achieved	13 months
Case 8	Stage 4		Asthma control could not be achieved	Omalizumab	13 months	Asthma control could not be achieved	12 months

Table IV: Changes in eosinophil count, IgE levels, FEV1, ACT, clinical condition, and presence of nasal polyps after treatment with mepolizumab.

	Eosinophil/mm ³	IgE IU/ML	FEV1	ACT	Clinically	Nasal polyps
Case 1	730→120 (after 12 months)	NA	400 ml (after 12 months)	21---25	Improved	No
Case 2	570→100 (after 12 months)	1500→550 (after 12 months)	870 ml (after 12 months)	18---24	Improved	No
Case 7	1670→140 (after 13 months)	2230→405 (after 13 months)	330 ml (after 13 months)	17---24	Improved	No
Case 8	300→0 (after 12 months)	1960→646 (after 12 months)	540 ml (after 12 months)	18---25	Improved	No

referral hospital, and considering the age of asthma onset (average 20.5 years), it suggests that our patients have late-onset asthma.

Allergic bronchopulmonary aspergillosis is a chronic allergic pulmonary disease that often requires long-term treatment. Methylprednisolone and itraconazole are commonly used medications, but long-term steroid use can lead to serious side effects such as osteoporosis, diabetes, cataracts, and myopathy (13). In our patients, we observed steroid-induced side effects including impaired blood glucose regulation, myopathy, and cataracts. To minimize the serious side effects of steroids, alternative treatment options have been explored.

Initially, all our patients received high-dose ICS+LABA+LTRA, methylprednisolone, and itraconazole. However, due to the inability to reduce steroid doses or steroid side effects, a biological agent was added to their treatment regimen. Despite these efforts, asthma control could not be achieved in all patients, necessitating the search for additional treatment options. Omalizumab was initiated in all patients due to inadequate asthma symptom control and asthma attacks. Previous literature has shown that omalizumab treatment reduces serum IgE levels, ABPA exacerbations, and steroid requirements, while improving asthma symptoms and increasing pulmonary function test parameters (14). Aydin et al. reported perfect effectiveness of omalizumab in 78.6% of ABPA patients and partial effectiveness in 21.4% (15). In a study conducted in our country, omalizumab treatment improved asthma symptoms and increased the mean asthma control test score in both the first and third years (16). In another study conducted in our country, omalizumab treatment improved asthma symptoms and increased the mean asthma control test score in both the first and third years (17). Although most of our ABPA patients responded well to omalizumab, some required alternative treatments.

In our study, 50% of the patients needed an alternative agent due to poor asthma symptom control and attacks, and we switched them from omalizumab to mepolizumab. However, we continued treating the remaining 50% with omalizumab. While literature reports a single patient receiving simultaneous treatment with omalizumab and mepolizumab (18), we did not have any patients receiving both agents concurrently. Among our patients who were switched to mepolizumab, none experienced ABPA recurrence. Although our study had a small sample size, we observed no recurrence of ABPA in the four patients treated with mepolizumab.

All patients received mepolizumab at a dose of 100 mg every four weeks, consistent with previous case reports (6,19,20). Despite the small number of patients, considering the absence of ABPA attacks in our patients over one year with this dose, we recommend conducting a larger study to evaluate the efficacy of 100 mg every four weeks in a larger patient population.

The dose of omalizumab was calculated based on the patient's total IgE level, following the recommended dosing table provided by the manufacturer. If the total IgE level was above 1500 KU/L, a dose of 375 mg every 14 days was initiated (8,21). Voskamp et al. administered omalizumab at a dose of 375 mg every 14 days in their 13-patient study and observed a reduction in exacerbations compared to placebo (22).

It is recommended to wait at least 32 weeks to evaluate the frequency of asthma attacks when using biologic agents (9). In our study, the evaluation period was 52 weeks, allowing for a comprehensive assessment of patient outcomes.

Patients who switched from omalizumab to mepolizumab showed improvements in FEV1, asthma control test scores, and reductions in total IgE and eosinophil

count. However, it is difficult to attribute these changes solely to mepolizumab as direct switching between biologic agents was performed without a period of no biologic agent usage.

In conclusion, ABPA should be considered in patients with asthma. When ABPA is diagnosed in patients receiving inhaler therapy for asthma, oral methylprednisolone and itraconazole are added to the treatment regimen. Alternative treatments should be considered if disease control cannot be achieved, steroid doses cannot be reduced, or steroid-related side effects develop.

Limitations of our study include the small number of cases reviewed. Further research in the form of randomized, double-blind clinical trials is needed to evaluate the efficacy and adverse effects of mepolizumab and omalizumab in ABPA. Additionally, the suitability of patients still using methylprednisolone while on omalizumab for switching to mepolizumab should be examined.

Consent for Publication

We obtained informed consent from all the patients who are still under our clinic's follow-up.

Availability of Data and Materials

The authors are open to sharing the data upon request.

Funding

This research did not receive any specific grants from public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflicts of interest.

Authors' Contributions

All authors contributed to the conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and original draft writing of the study.

Acknowledgments

The authors would like to express their gratitude to their families, colleagues, and co-authors who have contributed to this study.

Ethical Approval

Ethics committee approval of the University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital was obtained for this study.

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