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Effectiveness and Safety of Omalizumab in Patients with Allergic Bronchopulmonary Aspergillosis Complicated by Chronic Bacterial Infection in the Airways

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Keywords
Allergic bronchopulmonary aspergillosis · Anti-IgE antibody · Chronic respiratory infection · Nontuberculous mycobacteria · *Pseudomonas aeruginosa*

Abstract
Background: Allergic bronchopulmonary aspergillosis (ABPA) develops in the presence of predisposing conditions such as asthma and cystic fibrosis. Even ABPA accompanied by asthma is often complicated by chronic *Pseudomonas aeruginosa* or nontuberculous mycobacterial infection of the lower respiratory tract, rendering treatment with corticosteroids difficult. There have been several reports on the effectiveness of omalizumab, an anti-IgE antibody, in patients with ABPA. We analyzed the effectiveness and adverse effects of omalizumab in ABPA patients with chronic respiratory infections. ***Methods:*** Using our nationwide survey database and published case reports, we identified patients with severe asthma and ABPA who fulfilled the International Society for Human and Animal Mycology criteria and who had been treated with omalizumab. Exacerbation rates, control of symptoms, doses of oral corticosteroids, and pulmonary function were evaluated. ***Results:*** Among 25 patients with ABPA treated with omalizumab (median age 62 years, range 33–83 years), 12 patients had a chronic bacterial infection of the lower airways attributable to *P. aeruginosa* ($n = 6$) or nontuberculous mycobacteria ($n = 6$) at the initiation of omalizumab. Treatment with omalizumab reduced the frequency of exacerbations and systemic corticosteroid doses and improved pulmonary function. There were no significant adverse events or worsening of infection during treatment with omalizumab, except for injection-site reactions. ***Conclusions:*** Treatment with omalizumab was effective and safe in patients with ABPA, regardless of comorbid chronic respiratory tract infections.

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a disorder caused by hypersensitivity to and colonization of *Aspergillus fumigatus* in the airways of patients with asth-

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ma or cystic fibrosis [1, 2]. The patients present with various clinical and radiologic manifestations, such as worsening of asthmatic symptoms, cough and viscous phlegm, recurrent pulmonary infiltrates, bronchiectasis, and mucus plugs in the central bronchi. Worldwide, it has been estimated that 2.5% of patients with asthma develop ABPA [3].

Management of ABPA consists of pharmacotherapy with systemic corticosteroids and/or antifungal drugs. Although disease remission can be achieved in most cases with medium- to high-dose systemic corticosteroids, relapses occur in a substantial proportion of patients (13.5–45%) often repeatedly and, eventually, these patients become corticosteroid dependent [4, 5]. In our nationwide survey of ABPA in Japan [6], 75% of affected patients were treated with systemic corticosteroids, and approximately half of them required these agents for more than a year. Such long-term use of corticosteroids can cause a variety of adverse effects, including diabetes mellitus, osteoporosis, cataracts, glaucoma, and opportunistic infections [7].

Lower respiratory tract infections are almost inevitable in ABPA cases complicated by cystic fibrosis [8], although a substantial proportion of patients with ABPA develop chronic respiratory infection in the absence of cystic fibrosis. These patients are especially vulnerable to *Pseudomonas aeruginosa* [9, 10] or nontuberculous mycobacteria [11–13] because of the combined effects of structural deformities in the airways and compromised immunity caused by systemic and local administration of corticosteroids.

Omalizumab, a humanized monoclonal antibody against IgE [14], exhibits excellent therapeutic effects in patients with allergic asthma, including suppression of exacerbations and reduction of the total dose of corticosteroids administered [15, 16]. Several case reports and case series [17, 18], as well as a small randomized controlled trial [19], have demonstrated the effectiveness of omalizumab in patients with ABPA. In our nationwide survey of ABPA in Japan, approximately 6% of patients with ABPA, who were complicated by severe asthma, were treated with omalizumab [6]. We further explored the clinical characteristics of these patients treated with omalizumab and found that a substantial proportion of patients had a chronic respiratory infection caused by nontuberculous mycobacteria or *P. aeruginosa* at the initiation of omalizumab treatment. Therefore, we performed a detailed analysis of the effectiveness and adverse effects of omalizumab in this population in more detail.

Methods

Subjects

A retrospective cross-sectional survey of ABPA and allergic bronchopulmonary mycosis (ABPM) was conducted in 2013 involving more than 900 Japanese institutions certified by the Japanese Respiratory Society or the Japanese Society of Allergology as previously reported [6]. From this survey, we recruited patients with ABPA who were treated with omalizumab for concomitant severe asthma. In addition, physicians who reported Japanese cases of ABPA treated with omalizumab were invited to participate in this study. All clinical data were retrospectively collected from medical records and by questionnaires to the physicians.

ABPA was diagnosed based on the following International Society for Human and Animal Mycology criteria [1]: (1) immediate cutaneous hyperreactivity upon exposure to *Aspergillus* antigen or *A. fumigatus*-specific IgE levels in serum ≥0.35 UA/mL and (2) total IgE levels in serum ≥1,000 IU/mL, with the presence of 2 or more of the following features: (a) precipitins or IgG specific for *A. fumigatus*, (b) radiographic findings in the lungs consistent with ABPA, and (c) a total eosinophil count in peripheral blood ≥500 cells/μL. A patient who meets all the criteria, that is, from (a) to (c), can be diagnosed with ABPA even when the total IgE is <1,000 IU/mL. Chronic respiratory infection was defined based on chronic respiratory symptoms such as cough and/or phlegm for more than 3 months, and at least 2 positive sputum cultures or at least 1 positive bronchial washing or lavage culture of *P. aeruginosa* or nontuberculous mycobacteria.

The study was approved by the Institutional Review Board of Tokai University Hospital (#18R-068) and carried out in accordance with the principles embodied in the Declaration of Helsinki of 1965 as revised in 2013 in Brazil. The need for informed patient consent was waived for this study, given the anonymity of the data and the retrospective observational nature of the study.

Treatment with Omalizumab

Omalizumab was administered subcutaneously every 2 or 4 weeks with dose adjustments based on body weight and total serum IgE levels at baseline. The optimal dose was calculated based on the dosing table approved in 2009, with a maximum dose of 375 mg per 2 weeks [20]. Evaluation of clinical effects was performed 16 weeks after the initiation of treatment.

The reasons for initiating and discontinuing omalizumab were investigated using the physician-administered questionnaire and the dose and duration of treatment based on medical records. The reasons for the initiation of omalizumab were categorized as (1) worsening of symptoms, (2) deterioration of radiographic findings, and (3) the need to avoid or reduce the dose of systemic corticosteroids. The reasons for discontinuation were categorized as (1) insufficient clinical effects, (2) adverse effects, and (3) other reasons such as economic reasons.

Treatment Effects and Safety

Therapeutic effects were examined in cases treated with omalizumab for at least 16 weeks. Adverse effects were evaluated in all patients treated with the drug, at least once.

The evaluation of clinical effects included (1) control of respiratory symptoms at 16 weeks of treatment as assessed by the physicians' global evaluation of treatment effectiveness, (2) exacerbation rates during the 16 weeks before and after the treatment with omalizumab,

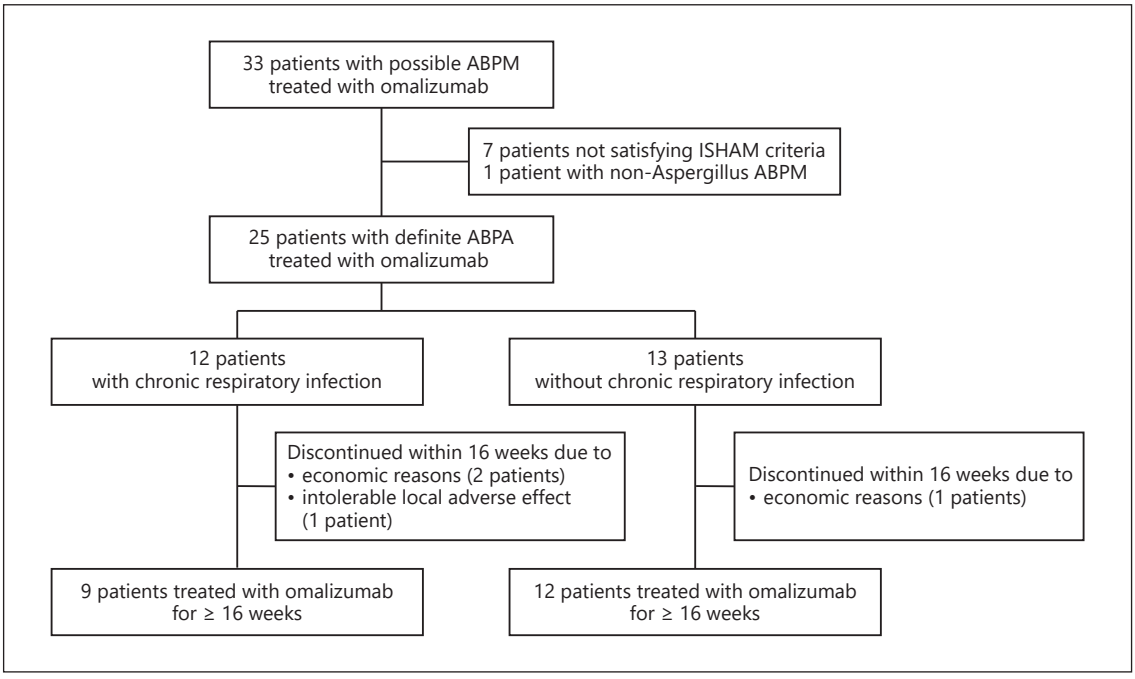

Fig. 1. CONSORT diagram demonstrating the flow of patients in the study. ABPA, allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycosis; ISHAM, International Society for Human and Animal Mycology.

and (3) dose of oral corticosteroid at baseline and 16 weeks after the treatment. Exacerbation was defined as the event that required administration of systemic corticosteroids or an increase in its dose.

Functional evaluation was performed by comparing forced expiratory volume in 1 s (FEV_1) measured within 6 months before and after treatment with omalizumab. Radiographic assessment of pulmonary consolidation and mucus plugs in the bronchi was performed using thoracic computed tomography.

Statistical Analyses

Numerical data are presented as median and interquartile range, and categorical data are presented as numbers and percentages. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test or Wilcoxon signed-rank test and analysis of covariance. Statistical analyses were performed using GraphPad Prism 5.0b (GraphPad Software, La Jolla, CA, USA) and IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p < 0.05$.

Results

Patient Profiles

Thirty-three cases with possible ABPM treated with omalizumab were registered from 20 clinical centers in Japan, and 25 of these cases met the International Society for Human and Animal Mycology diagnostic criteria for ABPA (Fig. 1). Twelve patients (48%) had lower respiratory tract infections (*P. aeruginosa* in 6 cases and nontuberculous mycobacteria in 6 cases).

Patient demographics and clinical characteristics are summarized in Table 1. All patients included had a history of asthma, and none had cystic fibrosis. The median age at the time of treatment with omalizumab was 62 years in both subgroups. The median serum IgE levels at the initiation of omalizumab treatment were 398 IU/mL in the group with a chronic respiratory tract infection and 433 IU/mL in the group without any such infection. All cases showed positive *A. fumigatus*-specific IgE or an immediate skin reaction to *A. fumigatus* antigen, and 23 cases (92%) were positive for *A. fumigatus*-specific precipitin. Nineteen patients (76%) were receiving treatment with systemic corticosteroids (of whom 18 patients had been receiving systemic corticosteroids for at least 4 months), and 11 patients (44%) were receiving treatment with antifungal drugs at the time of omalizumab initiation.

Omalizumab Treatment

The details of the omalizumab treatment are summarized in Table 2. The median dose of omalizumab was 300

Table 1. Demographic data on the studied subjects

	All cases	With infection	Without infection	*p* value
N (%)	25	12 (48)	13 (52)	
Age, years	62 (47–71)	62 (42–75)	62 (50–69)	0.98
Female, *n* (%)	15 (60)	8 (67)	7 (54)	0.69
History of asthma, *n* (%)	25 (100)	12 (100)	13 (100)	–
Laboratory data at diagnosis				
Peripheral blood eosinophil count, cells/μL	1,011 (680–1,590)	1,380 (924–2,962)	970 (495–1,262)	0.04
Serum IgE level, IU/mL	1,600 (500–4,327)	2,962 (588–7,077)	1,580 (500–2,083)	0.27
Specific IgE or immediate skin reaction to *A. fumigatus*, *n* (%)	25 (100)	12 (100)	13 (100)	–
Precipitin to *A. fumigatus*, *n* (%)	23 (92)	11 (92)	12 (92)	1.00
Laboratory data at omalizumab treatment				
Serum IgE level, IU/mL	411 (286–798)	398 (275–573)	433 (294–1,609)	0.38
Therapy at omalizumab treatment				
Inhaled corticosteroid dosage, μg budesonide/day (beclomethasone dipropionate equivalent, μg)	800 (440–1,000)	720 (500–1,000)	800 (400–1,000)	0.81
Oral corticosteroids, *n* (%)	19 (76)	8 (67)	11 (85)	0.38
Antifungal agents, *n* (%)	11 (44)	5 (42)	6 (46)	1.00
Antibiotics, *n* (%)	5 (20)*	5 (42)*	0 (0)	0.01
Concomitant chronic respiratory infection				
Pseudomonas aeruginosa, *n* (%)	6 (24)	6 (50)	–	–
Nontuberculous mycobacteria, *n* (%)	6 (24)	6 (50)	–	–

Values are medians (interquartile range) or *n* (%) of patients. * Three cases treated with the combination of clarithromycin, rifampicin, and ethambutol, and 2 cases treated with low-dose macrolides.

Table 2. Omalizumab treatment

	All cases	With infection	Without infection	*p* value
N (%)	25	12 (48)	13 (52)	
Weight, kg	53 (42–61)	46 (38–52)	57 (51–64)	0.06
Serum IgE level, IU/mL	411 (286–798)	398 (275–573)	433 (294–1,609)	0.38
Omalizumab dose, mg/4 weeks	450 (263–600)	450 (169–713)	300 (300–300)	1.00
Duration of omalizumab therapy, months	20 (7.5–45.5)	10 (4.0–26.3)	41 (15.5–54.5)	0.05
Patients treated with suboptimal dose of omalizumab, *n* (%)	10 (40)	3 (25)	7 (54)	
Reasons for initiation of omalizumab				
Worsening of symptoms, *n* (%)	25 (100)	12 (100)	13 (100)	–
Deterioration of radiographic findings, *n* (%)	10 (40)	3 (25)	7 (54)	0.23
Necessity to reduce or avoid systemic corticosteroids, *n* (%)	8 (32)	7 (58)	1 (8)	0.01
Reasons for discontinuation of omalizumab				
Insufficient clinical effects, *n* (%)	0 (0)	0 (0)	0 (0)	–
Adverse effects, *n* (%)	1 (4)	1 (8)	0 (0)	–
Others such as economic reasons, *n* (%)	3 (12)	2 (17)	1 (8)	–
Adverse effect				
Anaphylaxis, *n* (%)	0 (0)	0 (0)	0 (0)	–
Injection-site reaction, *n* (%)	1 (4)	1 (8)	0 (0)	–

Values are medians (interquartile range) or *n* (%) of patients.

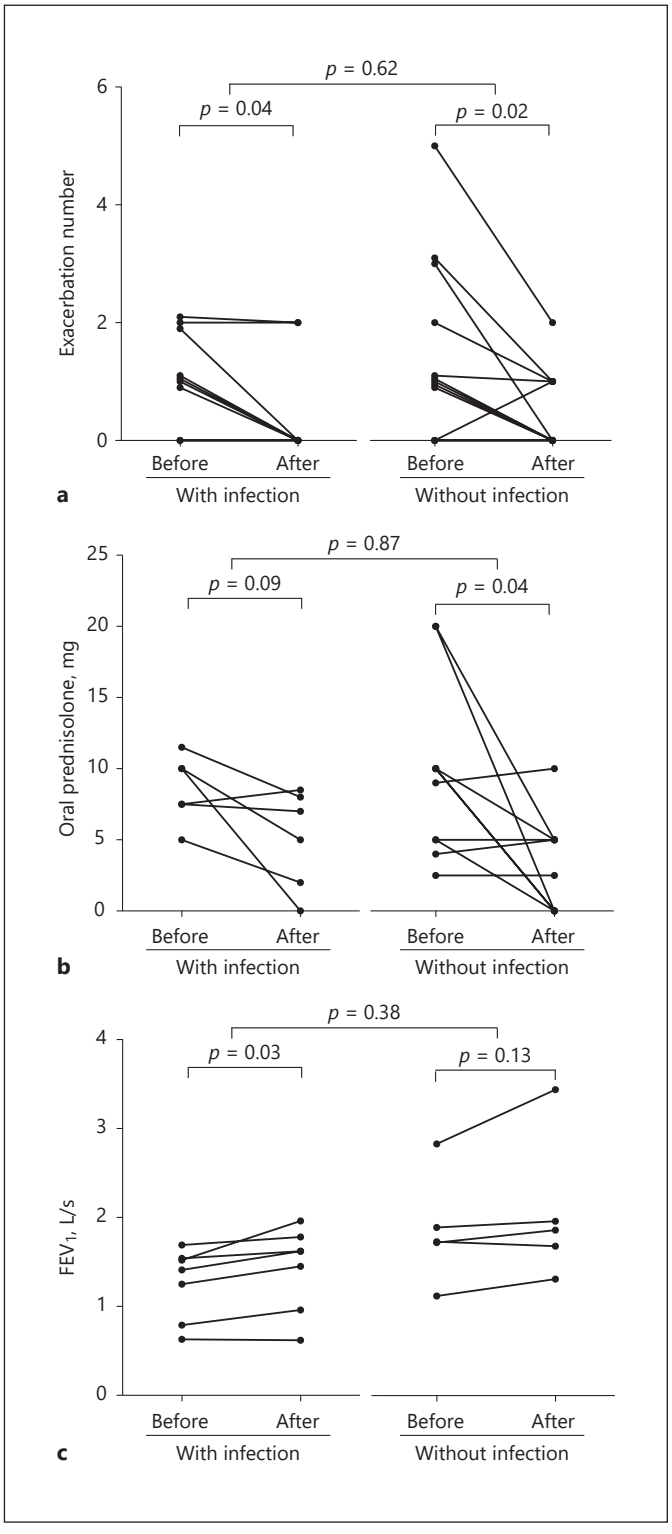

Fig. 2. Number of exacerbations within 4 months (**a**, $n = 21$), doses of oral prednisolone (**b**, $n = 16$), and FEV_1 (**c**, $n = 12$) before and after initiating treatment with omalizumab in patients with severe asthma and ABPA. ABPA, allergic bronchopulmonary aspergillosis; FEV_1, forced expiratory volume in 1 s.

mg per 4 weeks, and the median duration of treatment was 20 months. According to the dosing table predetermined in 2009, the dose of omalizumab administered was noted to be suboptimal in 10 cases, including 7 cases with baseline serum IgE levels >700 IU/mL, the upper limit for treatment with omalizumab. There was no significant difference in the dose of omalizumab between patients with and without chronic respiratory infection, but the duration of treatment was significantly shorter in the group with an infection (10 vs. 41 months, $p = 0.04$).

Before omalizumab initiation, worsening of respiratory symptoms was observed in all cases and worsening radiographic findings in 10 cases (40%). The necessity to reduce or avoid oral corticosteroids was an incentive for physicians to start omalizumab more frequently in patients with chronic respiratory infection than in those without (58 vs. 8%, $p < 0.01$).

Clinical Outcomes

Omalizumab was discontinued within 16 weeks in 3 cases due to patient-related economic reasons and in 1 case because of an intolerable local adverse effect. Thus, the clinical outcomes were evaluated in 21 patients treated with omalizumab for ≥16 weeks.

Good or excellent responses according to the global evaluation of treatment effectiveness assessment were reported at 16 weeks of omalizumab treatment in 7 of 9 patients (78%) with chronic infection and all 12 patients without such an infection (100%, $p = 0.17$). There was a significant reduction in the exacerbation rate during the first 4 months of omalizumab treatment compared with the rate seen in the immediate 4 months before treatment ($p < 0.01$). These effects were observed regardless of the presence ($p = 0.04$) or absence ($p = 0.02$) of chronic respiratory infections, showing no significant differences between groups ($p = 0.62$, Fig. 2a).

In the 16 patients treated with maintenance doses of oral corticosteroids at baseline, the median dose of prednisolone was reduced from 9.5 to 5 mg ($p < 0.01$). Among the 6 patients with a chronic respiratory infection, the dose of oral corticosteroids was reduced in 5 patients (83%), and the median dose of prednisolone was reduced from 8.8 to 6.0 mg ($p = 0.09$, Fig. 2b). The corticosteroid dose was also reduced in 5 (56%) of 9 patients without infections, and there were no significant differences between the groups. Antifungal drugs were discontinued in 4 of 9 patients after treatment with omalizumab.

The effects on pulmonary function were analyzed in 12 patients whose spirometry data before and after omalizumab treatment were available, 7 with a chronic respi-

ratory infection and 5 without. In the subjects with chronic respiratory infections, pretreatment FEV_1 was significantly lower (1.26 L/s) than in those without infections (1.86 L/s, $p < 0.01$), but FEV_1 was modestly, although significantly, improved after omalizumab treatment ($p = 0.03$, Fig. 2c).

Among the 10 patients who presented with radiographic worsening at baseline, 5 (50%) showed radiographic improvements after omalizumab initiation; 5 cases had resolution of consolidation and 3 cases had disappearance of mucus plugs, all of whom were without a chronic respiratory infection. None of the 3 patients with a chronic respiratory infection exhibited radiographic improvement after omalizumab treatment.

Safety

There were no severe adverse events, including episodes of anaphylaxis, during treatment with omalizumab. One patient developed an injection site reaction, leading to discontinuation of treatment 2 weeks after initiation. There were no cases of worsening of a lower respiratory tract infection after omalizumab initiation.

Discussion

This is the first study to investigate the clinical effectiveness and safety of omalizumab in patients with ABPA complicated by chronic respiratory infections caused by *P. aeruginosa* or nontuberculous mycobacteria. Omalizumab treatment demonstrated significant clinical responses, including a reduction in the frequency of exacerbations, a reduction in the dose of oral corticosteroids, and improvement of pulmonary function. Omalizumab also had an acceptable safety profile and was well-tolerated without any worsening of chronic respiratory infections.

Non-cystic fibrosis ABPA is often complicated by chronic *P. aeruginosa* or nontuberculous mycobacterial infection of the lower respiratory tract. Ishiguro et al. [12] reported that 7 (17%) of 42 patients with ABPM developed a nontuberculous mycobacterial infection and 21 (50%) had chronic lower respiratory tract infections caused by *Staphylococcus aureus* or *P. aeruginosa*. The presence of bronchiectasis and the use of high-dose corticosteroids administered by inhalation or systemically to treat ABPA are the possible predisposing factors for respiratory infections in these cases. In our study, 12 patients (48%) had a chronic respiratory infection caused by *P. aeruginosa* (6 cases) or nontuberculous mycobacteria (6 cases), all of whom were treated with moderate- to high-dose inhaled corticosteroids and two-thirds were treated with systemic corticosteroids.

Such a high prevalence of concomitant respiratory infection in asthmatics with ABPA has not been reported outside Japan. One of the possible reasons for the higher prevalence of chronic respiratory infections might be that Japanese patients with ABPA are older, as previously reported by us and other researchers. The median age of patients with ABPA was in the 30s in the studies conducted in India [21] but was in the 50s or 60s in those conducted in Japan [6] and Korea [22]. In the present study, the median patient age at diagnosis of ABPA was 52 years, and the median age at the time of treatment with omalizumab was 62 years. These patients with late-onset ABPA might be more vulnerable to chronic respiratory infections.

The standard option for the treatment of ABPA is oral corticosteroids, azole class of antifungal agents, or their combination; however, these treatments can be compromised in the presence of chronic respiratory infections. Administration of systemic corticosteroids is highly likely to worsen the infection with *P. aeruginosa* or nontuberculous mycobacteria, and the use of azole antifungals is hindered by drug interactions with rifampicin and macrolides. Clinical outcomes of ABPA cases co-treated with antibiotics and systemic corticosteroids are inconsistent [23, 24]. In contrast, omalizumab does not exhibit immunosuppressive effects except for helminthic or other parasitic infections, and there have been no reports that omalizumab has any drug interaction with the azole class of antifungal agents.

Treatment with omalizumab led to clinical and functional improvements, regardless of the presence of chronic respiratory infection; however, radiographic improvements were not observed in the 3 patients with radiographic worsening at the initiation of omalizumab treatment. This might be due to the difficulty in differentiating whether the radiographic changes are caused by ABPA exacerbation or a concomitant infection. The optimal choice of treatment for ABPA with concomitant chronic respiratory infections might be more important for cases with cystic fibrosis; however, a multicenter, double-blinded, placebo-controlled trial of omalizumab in patients with cystic fibrosis and ABPA had been terminated prematurely due to poor enrollment. In addition, based on a systematic review, the use of omalizumab in patients with ABPA and cystic fibrosis is not recommended owing to the absence of validated data [25]. Further analysis with an increased number of cases would be required to fully elucidate the effects of omalizumab on the clinical and pathological changes of ABPA.

Our study has several limitations. First, it is a retrospective observational study, which might have introduced a degree of selection bias leading to the overestimation of the effectiveness of omalizumab. Second, the effectiveness was evaluated 4 months after the initiation of omalizumab, and the long-term effects of this agent have not been confirmed. Third, although 20% of the patients with ABPA do not present with asthma [6], there were no data on omalizumab use in such patients because ABPA without severe asthma is not an indication for the drug. Therefore, a prospective randomized controlled trial is needed to confirm the effects of omalizumab in patients with ABPA with or without asthma.

Conclusion

In patients with ABPA, treatment with omalizumab improves clinical outcomes such as the exacerbation rate, oral corticosteroid doses, and pulmonary functions even when they were complicated with chronic respiratory infection. Omalizumab treatment, which can prevent the use or reduce the doses of systemic corticosteroids, may be an especially good choice of treatment in ABPA patients with chronic respiratory infections.

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Statement of Ethics

The study was approved by the Institutional Review Board of Tokai University Hospital (#18R-068) and carried out in accordance with the principles embodied in the Declaration of Helsinki of 1965 as revised in Brazil 2013. The need for informed patient consent was waived for this study by the Institutional Review Board in view of the anonymity of the data and the retrospective observational nature of the study.

Disclosure Statement

M.T. has received lecture fees from AstraZeneca and GlaxoSmithKline. T.B. has received lecture fees from Boston Scientific. K.A. has received lecture fees from AstraZeneca, Astellas Pharma, Kyorin Pharma, MSD, and Novartis Pharma.

Author Contributions

K.T. and K.A. contributed to the conception and design of the study, and analysis and interpretation of data. O.T., M.T., and the members of the Japan ABPM Research Program contributed to the conduct of the study and data collection. K.T. wrote the manuscript. All the authors have agreed to be accountable for all aspects of the study and have approved the final version of the manuscript.

References

1 Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013 Aug;43(8):850–73.

2 Asano K, Kamei K, Hebisawa A. Allergic bronchopulmonary mycosis: pathophysiology, histology, diagnosis, and treatment. Asia Pac Allergy. 2018 Jul;8(3):e24.

3 Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol. 2013 May;51(4):361–70.

4 Patterson R, Greenberger PA, Halwig JM, Liotta JL, Roberts M. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. Arch Intern Med. 1986 May;146(5):916–8.

5 Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in North India. Chest. 2006 Aug; 130(2):442–8.
6 Oguma T, Taniguchi M, Shimoda T, Kamei K, Matsuse H, Hebisawa A, et al. Allergic bronchopulmonary aspergillosis in Japan: a nationwide survey. Allergol Int. 2018 Jan;67(1): 79–84.
7 Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006 Jun 15;55(3):420–6.
8 Geller DE, Kaplowitz H, Light MJ, Colin AA. Allergic bronchopulmonary aspergillosis in cystic fibrosis: reported prevalence, regional distribution, and patient characteristics. Scientific Advisory Group, Investigators, and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Chest. 1999 Sep;116(3):639–46.
9 Ionescu MD, Balgradean M, Marcu V. Allergic bronchopulmonary aspergillosis in patient with cystic fibrosis: a case report. Maedica. 2014 Dec;9(4):387–90.
10 Reece E, Segurado R, Jackson A, McClean S, Renwick J, Greally P. Co-colonisation with Aspergillus fumigatus and *Pseudomonas aeruginosa* is associated with poorer health in cystic fibrosis patients: an Irish registry analysis. BMC Pulm Med. 2017 Apr 21;17(1):70.
11 Ishiguro T, Takayanagi N, Takaku Y, Kagiyama N, Shimizu Y, Yanagisawa T, et al. Allergic bronchopulmonary aspergillosis with repeated isolation of nontuberculous mycobacteria. Intern Med. 2013;52(15):1721–6.
12 Ishiguro T, Takayanagi N, Baba Y, Takaku Y, Kagiyama N, Sugita Y. Pulmonary nontuberculous mycobacteriosis and chronic lower respiratory tract infections in patients with allergic bronchopulmonary mycosis without cystic fibrosis. Intern Med. 2016;55(9):1067–70.
13 Tsubouchi H, Tsuchida S, Yanagi S, Shigekusa T, Miura M, Sakaguchi K, et al. Successful treatment with mepolizumab in a case of allergic bronchopulmonary aspergillosis complicated with nontuberculous mycobacterial infection. Respir Med Case Rep. 2019;28: 100875.
14 Presta LG, Lahr SJ, Shields RL, Porter JP, Gorman CM, Fendly BM, et al. Humanization of an antibody directed against IgE. J Immunol. 1993 Sep 1;151(5):2623–32.
15 Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): innovate. Allergy. 2005 Mar;60(3):309–16.
16 Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med. 2011 May 3; 154(9):573–82.
17 Perez-de-Llano LA, Vennera MC, Parra A, Guallar J, Marin M, Asensio O, et al. Effects of omalizumab in *Aspergillus*-associated airway disease. Thorax. 2011 Jun;66(6):539–40.
18 Homma T, Kurokawa M, Matsukura S, Yamaguchi M, Adachi M. Anti-IgE therapy for allergic bronchopulmonary aspergillosis. J Microbiol Immunol Infect. 2016 Jun;49(3): 459–63.
19 Voskamp AL, Gillman A, Symons K, Sandrini A, Rolland JM, O'Hehir RE, et al. Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract. 2015 Mar–Apr;3(2):192–9.
20 Hochhaus G, Brookman L, Fox H, Johnson C, Matthews J, Ren S, et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. Curr Med Res Opin. 2003;19(6):491–8.
21 Chakrabarti A, Sethi S, Raman DS, Behera D. Eight-year study of allergic bronchopulmonary aspergillosis in an Indian teaching hospital. Mycoses. 2002 Oct;45(8):295–9.
22 Kim JH, Jin HJ, Nam YH, Hwang EK, Ye YM, Park HS. Clinical features of allergic bronchopulmonary aspergillosis in Korea. Allergy Asthma Immunol Res. 2012 Sep;4(5):305–8.
23 Mussaffi H, Rivlin J, Shalit I, Ephros M, Blau H. Nontuberculous mycobacteria in cystic fibrosis associated with allergic bronchopulmonary aspergillosis and steroid therapy. Eur Respir J. 2005 Feb;25(2):324–8.
24 Kadamkulam Syriac A, Malhotra G, Anez de Gomez CI, Copur AS. *Mycobacterium avium* intracellulare infection complicated by allergic bronchopulmonary aspergillosis in a non-asthmatic patient. BMJ Case Rep. 2018 May 26;2018:bcr2018224835.
25 Jat KR, Walia DK, Khairwa A. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev. 2018 Mar 18;3:CD010288.