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Elif Tuğçe Korkmaz, Ömür Aydın, Dilşad Mungan, Betül Ayşe Sin, Yavuz Selim Demirel, Sevim Bavbek

Can dose reduction be made in patients with allergic bronchopulmonary aspergillosis receiving high-dose omalizumab treatment?

Division of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey

Key words

Omalizumab; ABPA; asthma; asthma control; omalizumab dose reduction.

Corresponding author
Sevim Bavbek
Division of Immunology and Allergy
Department of Chest Diseases
Ankara University School of Medicine
Balkiraz District, Tıp Fakültesi Caddesi No: 1/4
06620 Mamak, Ankara, Turkey
ORCID: 0000-0002-7884-0830
E-mail: bavbek@medicine.ankara.edu.tr

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Impact statement

Decreasing the total monthly omalizumab dose either by the same or extended time interval does not cause clinical deterioration in patients with ABPA after the disease is controlled.

Summary

Background. *Allergic bronchopulmonary aspergillosis (ABPA) is an endotype of severe asthma which frequently needs biologics for their steroid sparing effect. We aimed to evaluate the outcomes of reducing the omalizumab dose in patients with ABPA who were on long-term omalizumab treatment.* ***Methods.*** *Once asthma was controlled, two approaches were used to reduce total monthly omalizumab dose: 1) both extending dose intervals from 2 to 4 weeks and decrease omalizumab dose, 2) to reduce omalizumab dose while keeping dose intervals stable.* ***Results.*** *Thirteen patients with ABPA (8F/5M, mean age 53.4 ± 13.0 years) were included. Pre-omalizumab, mean numbers of attacks and hospitalizations were 2.5 ± 1.5 and 1.3 ± 0.8, mean oral corticosteroid (OCS, as methylprednisolone) dose was 12.2 ± 10.4 mg daily. First omalizumab dose reduction was made to all patients at a median time of 35 months (min 13, max 47). The 2nd dose reduction was made in four patients at median of 23.5 months. Mean OCS decreased to 0.69 ± 0.95 mg/day (p = 0.001) in the 1st year of omalizumab, could be stopped in 11 patients in last evaluation. Attacks/hospitalizations decreased significantly to 0.31 ± 0.86 and 0, respectively, in the 1st year of omalizumab. Total omalizumab dose was reduced by median 40% (min 20, max 60) in 1st intervention and 50% (min 20, max 67) after 2nd intervention. After omalizumab dose reduction, asthma control did not deteriorate and there was no need to increase the omalizumab or OCS-dose.* ***Conclusions.*** *Decreasing the total omalizumab dose does not cause clinical deterioration in ABPA after the disease is controlled.*

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease with a wide clinical spectrum: asthma, bronchiectasis, and if left untreated, it results in pulmonary fibrosis to destructive pulmonary disease (1). ABPA treatment aims to achieve asthma control, to prevent attacks and the development of bronchiectasis and pulmonary fibrosis (2). In ABPA, which is associated with high IgE levels, one of the current treatment alternatives is omalizumab especially in oral corticosteroid (OCS)-dependent patients with adverse effects due to steroid use. Omalizumab (Xolair; Genentech and Novartis, South San Francisco, CA) is the first approved biological in patients with severe allergic asthma because of established efficacy and safety in this group (3, 4). Published data demonstrated that omalizumab was also effective in reducing exacerbations and OCS requirements and improving asthma symptoms and pulmonary function parameters in patients with asthma and ABPA

who had previously shown an unsatisfactory response to inhaled corticosteroids (ICS) and OCS (2, 3, 5, 6).
We started using omalizumab since 2008, first in the treatment of severe allergic asthma and then in patients with ABPA. In keeping with that, we reported our first experience with omalizumab on 14 patients with a diagnosis of ABPA (6). In this study, patients were on omalizumab for a mean of 31.5 months, which was the longest follow-up period reported to date. Since then, we continued prescribing omalizumab in new patients with ABPA. Further considering the high cost, we attempted to reduce the omalizumab dose in patients with ABPA who were on long-term omalizumab treatment. In the present paper, we aimed to share our experience with this approach.

Materials and methods

Study population

The study was conducted as a retrospective chart review of patients with asthma and ABPA who were treated with omalizumab at the Department of Chest Diseases, Division of Clinical Immunology and Allergy, Faculty of Medicine. The charts were reviewed by three physicians. The local Ethics Committee of Faculty of Medicine approved the study and informed consent was obtained from all the subjects (Ethics Committee Approval no: I4-230-20, date: April 29, 2020).
In the diagnosis of ABPA, the diagnostic criteria determined by Agarwal *et al*. were used (2). A total of 13 patients with ABPA, who had undergone treatment with omalizumab injections between December 2008 and March 2020 were included in the study. The patients were being followed up regularly and had complete health care coverage. Demographics and disease characteristics were recorded from patient files (**table I**). All patients were receiving OCS (as methylprednisolone) with other controller medications including high-dose ICS and long-acting beta 2 agonist.

Measurements

After treatment with omalizumab was started, data including forced expiratory volume in first second (FEV1), asthma control test (ACT) scores, eosinophil count and dose of OCS, for asthma were collected at baseline, first year, and the last evaluation. Outcome measurements are detailed in **figure 1**. The number of asthma exacerbations and hospitalizations for 1 year prior to omalizumab and yearly after starting omalizumab were also recorded. To evaluate the response to omalizumab treatment, patients with ABPA were classified as "complete responders", "partial responders" and "non-responders". If the patient's asthma was under control, with no asthma attack or asthma-related hospitalization in the last 1 year of treatment, and ACT ≥ 20 and this was accompanied by a at least 25% decrease in OCS dose or an improvement at least 200 ml increase in FEV1, these patients were accepted as "complete responders". If at least one of complete control parameters could not be reached, they were accepted as "partial responders". Patients who did not meet any of complete control parameters were considered "non-responders".

Table I *- Demographic and clinical characteristics of the patients before initiation of omalizumab treatment for the first time.*

Variables	Mean ± SD (min-max)
n	13
Sex (female)	8
Age, year	53.4 ± 13.0 (31-69)
Disease duration of asthma, years	19.4 ± 8.4 (9-34)
ABPA diagnosis time, years	10.2 ± 3 (3.5-13)
Body weight, kg	74.5 ± 18.8 (49-105)
Total IgE, IU/mL	821.9 ± 494.8 (356-2,030)
Blood eosinophil count, (cells/mcL)	723.1 ± 547.1 (100-2,200)
FEV1, %	63.0 ± 17.0 (40-100)
FEV1, mL	1876.2 ± 606.7 (1,000-2,970)
FEV1/FVC, %	67.7 ± 13.1 (49-90)
ACT score	15.7 ± 3.5 (11-22)
OCS dose (mg) (methylprednisolone)	12.2 ± 10.4 (4-40)
Number of asthma attacks/year (in the previous year before starting omalizumab treatment)	2.5 ± 1.5 (1-6)
Number of hospitalizations/year (in the previous year before starting omalizumab treatment)	1.3 ± 0.8 (0-2)
Duration of omalizumab treatment, months	64.8 ± 24.2 (38-99) (median 63)
Total monthly omalizumab dose	median 750 (min 300-max 900)
300 mg (patient #9)	1
450 mg (patient #4)	1
600 mg (patient #1, 10)	2
750 mg (patient #2, 3, 6, 7, 8, 11, 12)	7
900 mg (patient #5, 13)	2

SD: standard deviation; min: minimum; max: maximum; ABPA: allergic bronchopulmonary aspergillosis; IgE: immunoglobulin E; FEV1: forced expiratory volume in first second; FVC: forced vital capacity; ACT: asthma control test; OCS: oral corticosteroid.

Study design

During omalizumab treatment, at least one year treatment with omalizumab, if once the disease was controlled, then one of the two approaches was initiated in order to reduce the total monthly dose of omalizumab. The first was to extend dose intervals from 2 weeks to 4 weeks and to decrease the total omalizumab dose used per month, the second approach was to reduce the omalizumab dose while keeping the dose interval stable. In some patients, two approaches were used sequentially if the patient tolerated the dose reduction and/or dose interval extension (**table II**, **figure 1**). If the patient was still a complete responder at the end of the third year of the treatment at the earliest, omalizumab could be discontinued. If the disease became uncontrolled after treatment cessation, omalizumab was restarted.

Statistical analysis

The statistical analysis was performed by using the SPSS version 22 software (SPSS Inc., Chicago, IL, USA). As descriptive statistics, quantitative variables were stated as mean ± standard deviation (SD) and median (minimum-maximum) values, and qualitative variables as number (n) and percentage (%). To examine the difference between two dependent quantitative variables, the paired-samples t-test was used if the assumptions of normal distribution were met, and the Wilcoxon Sign test was used if not. A value of $p < 0.05$ was considered statistically significant.

Results

Data from the total of 13 patients with ABPA who were treated with omalizumab and underwent dose reduction were evaluated. The baseline demographic and clinical characteristics of the patients are summarized in **table I** and patients with corresponding approaches along with current situation are summarized in **table II**. The clinical characteristics of each subject are shown in **table III**.

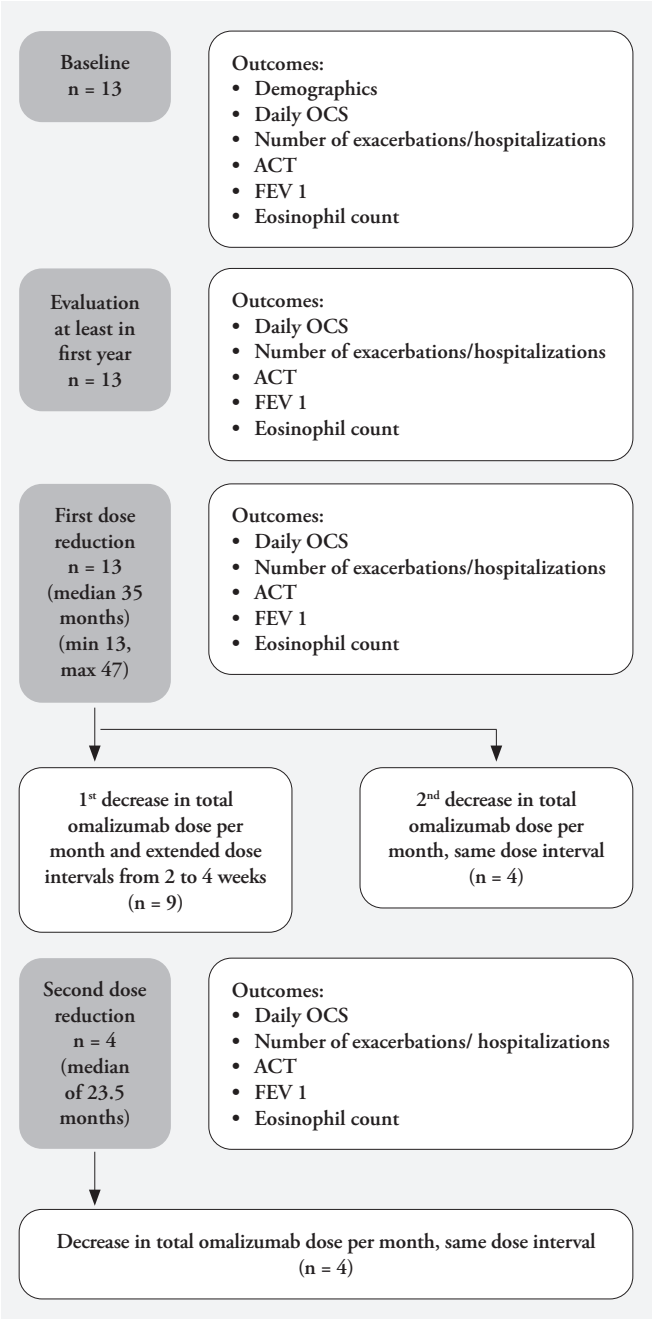
The mean time of dose reduction in omalizumab treatment was 33 ± 9.57 (median 35, minimum 13, maximum 47) months. The OCS used by the 13 patients before omalizumab treatment was 12.2 ± 10.4 mg/day. In the first year of omalizumab, the methylprednisolone dose decreased to 0.69 ± 0.95 mg/day with a mean dose of 0.25 ± 0.63 mg/day in the last evaluation of the dose-reduced patients, and methylprednisolone treatment could be stopped in 11 patients. Before omalizumab, the mean number of attacks was 2.5 ± 1.5 and the mean number of hospitalizations was 1.3 ± 0.8. In the first year of the treatment, the mean number of attacks decreased to 0.31 ± 0.86, and the mean number of hospitalizations decreased to 0. In the first year of omalizumab treatment, four patients (patient 1, 6, 9, 11) were complete responders, the remaining nine patients were partial responders.

The first approach, extension of dose intervals from 2 weeks to 4 weeks and decreasing the total omalizumab dose used per month, was used in patients 2, 3, 4, 5, 6, 8, 10, 12, 13. The second approach was used in patients 1, 7, 9, 11. In some patients (2, 5, 6, 13) two approaches were used sequentially if the patients tolerated the dose reduction and/or dose interval extension (**tables II**, **III**). The earliest dose reduction was done at 13th month (patient 5) in dose interval extended group (maximum 47th, median 35 months) in first dose reduction. The patient was receiving her omalizumab injections in her family physician's office because of the pandemic and had one asthma attack

Table II *- Details of management approaches.*

Approaches	Patients n at first attempt	Patients n at second attempt	Current situation in patients (n = 13)
Decrease in total omalizumab dose per month and extended dose intervals from 2 weeks (wk) to 4 weeks	n = 9 (#2, 3, 4, 5, 6, 8, 10, 12, 13)	-	n = 5 (#3: still in remission after omalizumab cessation for 18 months (last dose 300 mg/4 wk) #4: remission in 300 mg/4 wk #8: remission in 300 mg/4 wk #10, 12: in remission with 450 mg/4 wk omalizumab)
Decrease in total omalizumab dose per month, same dose interval	n = 4 (#1, 7, 9, 11)	n = 4 (#2, 5, 6, 13)	n = 8 (#1: remission in 450 mg/4 wk #2, 5, 6, 13: Remission in 300 mg/4 wk #7: was still in remission after omalizumab cessation for 10 months (last omalizumab dose was 300 mg/2 wk), then lost to follow-up from our clinic since 2014, but in her recent medical records she was not restarted omalizumab, she does not use oral steroid #9: remission in 150 mg/4 wk #11: remission in 300 mg/2 wk)

Figure 1 *- Flowchart of the study.*



requiring OCS, but she was devoid of OCS dose at 13th month. A second dose reduction was made in four patients (2, 5, 6, 13) at the minimum sixth month (patient 5) of the treatment (maximum 42nd, median 23.5 months).

In essence, the total omalizumab dose given per month was reduced in all 13 patients in both interventions. The total omalizumab dose given per month was reduced by a median of 40% (min 20, max 60%) in first intervention. After second intervention, the total dose reduction was a median 50% (min 20, max 67%).

In four patients (patients 4, 7, 9, 10), omalizumab was stopped before the fifth year. For patient 4, omalizumab was stopped at the third year, and two months after treatment cessation, OCS had to be restarted, so omalizumab was also restarted. For patient 7, omalizumab was stopped at the third year, and the patient was stable after treatment cessation, then she was lost to follow up, but from her electronic medical records, we learned that she was stable after omalizumab cessation. For patient 9, omalizumab was stopped at the third year of the treatment. Nineteen months after treatment cessation, the patient had three attacks, so omalizumab was restarted. For patient 10, omalizumab was stopped at the fourth year. Four months after treatment cessation, asthma control deteriorated, and OCS needed to be increased and omalizumab had to be restarted. In two patients, omalizumab treatment was given for longer than five years. For patient 6, omalizumab was stopped at the sixth year of the treatment, three months after treatment cessation asthma control was lost. Patient 8 discontinued omalizumab after the fifth year, four months after discontinuation of omalizumab he had dyspnea and deterioration in pulmonary function tests. In these two patients, omalizumab was again restarted and the patients responded well.

Discussion

In the present study, omalizumab treatment has been shown effective in treating patients with ABPA. Pre-omalizumab, mean OCS dose was 12.2 ± 10.4 mg daily, decreased to 0.69 ± 0.95 mg ($p = 0.001$) in the 1st year of omalizumab and could be stopped in 11 patients. 1 year prior to omalizumab, the mean numbers of attack and hospitalization were 2.5 ± 1.5 and 1.3 ± 0.8, respectively, and attacks and hospitalizations decreased to 0.31 ± 0.86 ($p < 0.001$) and 0 ($p = 0.003$), respectively, in the first year of omalizumab. Given the high cost of the drug and uncertainty in the long-term approach for omalizumab treatment in patients with ABPA, once the disease is under control, we attempted to decrease the dose of omalizumab by either extended intervals between doses or decreasing total doses or using both approaches. In these 13 patients whose omalizumab dose was reduced, there was no need to increase the omalizumab dose again, no need to increase the OCS dose, and despite that asthma remained under control.

Omalizumab was first licensed for severe allergic asthma patients with a total IgE level between 30-700 IU/mL at a maximum dose of 375 mg every two weeks (7). As a result of research on its use for higher IgE values (700-1,500 IU/mL) (7, 8) the dose table was updated for a maximum dose of 600 mg every 2 weeks

Table III *- Details of individual patients.*

Patient #, age, sex	Total IgE level	Initial number of attacks/ hospitalizations/ OCS (mg) (methylprednisolone)	Initial omalizumab dose	Dose reduction time 1 (months)	Reduced omalizumab dose time 1	Number of attacks/ hospitalizations/ OCS (mg) at first dose reduction	Dose reduction time 2 (months)	Reduced omalizumab dose time 2	Number of attacks/ hospitalizations/ OCS (mg) at second dose reduction or last evaluation
#1 61 y, M	567	2/0/8 mg	600 mg/4wk	37	450 mg/4wk	0/0/0 mg	Not done	-	0/0/0 mg
#2 61 y, F	400	2/2/6 mg	375 mg/2wk	35	450 mg/4wk	0/0/0 mg	35	300 mg/ 4wk	0/0/0 mg. Last evaluation 0/0/0 mg
#3 68 y, M	1512	4/1/20 mg	375 mg/2wk	45	300 mg/4wk	0/0/0 mg	Not done		0/0/0 mg
#4 43 y, F	356	1/1/40 mg	225 mg/2wk	42	300 mg/4wk	0/0/0 mg	Not done		0/0/0 mg
#5 53 y, F	1042	2/2/20 mg	450 mg/2wk	13	450 mg/4wk	1/0/0 mg	6	300 mg/ 4wk	0/0/0 mg
#6 33 y, M	588	2/2/16 mg	375 mg/2wk	22	300 mg/4wk	0/0/0 mg	42	150 mg/ 4wk	0/0/0 mg
#7 43 y, F	2030	1/1/4 mg	375 mg/2wk	27	300 mg/2wk	0/0/0 mg	Not done	Stopped	0/0/0 mg Then lost to follow up
#8 59 y, M	909	2/2/5 mg	375 mg/2wk	33	300 mg/4wk	0/0/0 mg	Not done		0/0/0 mg Then lost to follow-up
#9 57 y, F	482	4/2/10 mg	300 mg/4wk	24	150 mg/4wk	0/0/0 mg	Not done		0/0/0 mg
#10 69 y, F	491	4/2/5 mg	300 mg/2wk	37	450 mg/4wk	0/0/2 mg	Not done		0/0/2 mg
#11 31 y, M	1110	1/1/16 mg	375 mg/2wk	47	300 mg/2wk	0/0/2 mg	Not done		0/0/0 mg
#12 69 y, F	489	6/3/4 mg	375 mg/2wk	35	450 mg/4wk	1/1/0 mg	Not done		1/0/0 mg
#13 47 y, F	709	2/0/4 mg	450 mg/2wk	32	450 mg/4wk	0/0/0 mg	12	300 mg/ 4wk	1/0/0 mg Last evaluation 0/0/0 mg

(9, 10). Omalizumab for the treatment of ABPA has been evaluated in clinical studies (4, 11-14), and it is found to be beneficial in reducing exacerbations (4, 13), systemic steroid need, asthma symptoms, and respiratory parameters (4, 14). Omalizumab treatment is given at high doses in patients with ABPA due to high total IgE levels (10, 15, 16). In our first study, based on data in the literature, in 14 patients with ABPA, the dose of omalizumab was given at the highest recommended dose (375 mg every 2 weeks) and not based on the patient's weight and total IgE level (6). No dosing adjustments were made during the treatment period for this group. However, with the update of the recommended dosage table in omalizumab treatment, we changed treatment doses in new patients with ABPA accordingly. Our patients were given omalizumab treatment initially median total monthly dose of 750 mg (min 300, max 900), their mean total IgE level was 821.9 ± 494.8 IU/mL (min 356, max 2,030).

The resources needed for adding biological treatment to ABPA standard therapy are mainly driven by the cost of the drug. The other issue, which remains unresolved, is the duration of biological treatment in these patients as it is in asthma patients (2, 3, 17). In four patients (patients 4, 7, 9, 10), omalizumab was stopped before the fifth year. Three of them had to restart the treatment. In two patients, omalizumab treatment was given for longer than five years due to the loss of asthma control after treatment cessation. In these patients, omalizumab was again restarted and the patients responded well.

A few attempts have been done in patients with severe asthma and chronic urticaria, whether omalizumab can be withdrawn, or its dose be reduced in case of clinical improvement (18, 19). A recent paper evaluated the effects of extended intervals and dose reduction of omalizumab on asthma control in 37 patients with severe asthma in a real-life setting. The time intervals until loss of asthma control was compared and the authors reported that extension of omalizumab dose was a better approach than dose reduction after achieving asthma control (20). Similarly, in other study with 35 severe allergic asthma who are at least one and a half year of omalizumab treatment, omalizumab dose was reduced by half and if patients were clinically stable after 6 months, the dose was halved again. The study found that in more than 50% of asthma patients omalizumab dose can be safely reduced or withdrawn based on a progressive dose reduction protocol (18). However, there are no data in the literature regarding whether the reduction of the omalizumab dose or injection frequency leads to loss of control in patients with ABPA who receive high dose omalizumab (10) therefore we could not discuss our data comparing these studies but based on our results and results reported in severe allergic asthma patients the dose reduction seems to be possible.

Frequent (in every two weeks) omalizumab injections may affect personal and business life; it may also be associated with indirect expenses, such as travel expenses or loss of labor to go to the clinic for injections. Where it is possible to reduce the frequency of omalizumab injection every 4 weeks instead of every 2 weeks, patient burden and costs can be reduced (21). Lowe *et al.* (21) evaluated previous data of different omalizumab studies in asthma with a mathematical model because of the need for the evaluation of safety and efficacy of some doses of omalizumab given every 4 weeks at double doses instead of every 2 weeks according to the dosing table. They calculated that it would be hypothetically appropriate to reduce the recommended omalizumab dose frequency for some body weight and baseline IgE values. They found that free IgE suppression slightly increased in the initial phase, and slightly reduced at the trough of the dosing cycle, but the average suppression remained similar for both regimens. The safety profile of omalizumab was similar for patients receiving higher or lower doses. Therefore, they reported doubling the dose of omalizumab every 4 weeks instead of every 2 weeks, in a subset of patients (receiving 225-300 mg of omalizumab every two weeks), could efficiently suppress free IgE without compromising safety or efficacy (21). In literature, in a 63-year-old patient with house dust mite allergy and severe asthma, the omalizumab dose was reduced by half (375 mg/month instead of 750 mg/month) following long-term (3 years) use of omalizumab (22). In that report, serum free IgE level measurements were suggested to appropriately identify patients in whom the dose could be reduced, and to carefully monitor the clinical course (22). It was suggested that after months of omalizumab treatment, the IgE production rate might decrease, and the treatment could be discontinued by monitoring the total IgE level (23).

In our study, 13 patients with ABPA were evaluated, with a median duration of omalizumab use of 63 (min 38, max 99) months. To our best knowledge, this is the longest period among patients using omalizumab treatment with the diagnosis of ABPA. In the literature, patients with non-cystic fibrosis (CF) ABPA have been followed up until three years (24). Upon discontinuation of the omalizumab treatment, the disease was stable in some cases but worsened in others. In some patients with non-CF ABPA who are systemic steroid-dependent, discontinuation of omalizumab treatment could cause deterioration in asthma control (10). The results of our patients after discontinuation of treatment are concordant with these data. In six patients, after 3-5 years of omalizumab treatment, omalizumab was stopped. However, we had to restart omalizumab due to loss of asthma control within 2-19 months. Fortunately, these patients responded well to omalizumab, and asthma control was again achieved.

There are several limitations in our study. First, this is a small study with a limited number of patients. The second is the presence of two approaches instead of a standardized single approach to reach omalizumab dose reduction. Nevertheless, as a

real-life experience, our report proposes an innovative approach to omalizumab therapy in patients with ABPA. We believe that these data may have important clinical implications for the sustainability of this therapy in daily practice.

In conclusion, our real-life experience may suggest attempting to reduce monthly omalizumab dose in patients with ABPA after the disease has been controlled. However, there is clearly a need for controlled clinical trials with large number of patients to define in which ABPA patient is candidate for dose reduction and which approach can be more efficient to reduce omalizumab doses. If these reports support our experience, the possibility of lower cost and decreased hospital visits will encourage practicing physicians using omalizumab.

Fundings

None.

Contributions

ETK: data curation, writing - original draft, writing - review & editing. ÖA: conceptualization, study design, data curation, writing - original draft, writing - review & editing. DM, BAS, YSD: study design, writing - original draft, writing - review & editing. SB: conceptualization, study design, writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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