

Discontinuing Omalizumab Treatment in Super-Responder Patients with Allergic Severe Asthma: Can the Baseline Total IgE Level Be Used as a Biological Marker to Decide Discontinuing Omalizumab Treatment?

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Keywords

Allergic severe asthma · Omalizumab · Re-treatment · Discontinuation

Abstract

Background: Although there are many studies presenting the efficacy of omalizumab in severe asthma, the data about the optimal treatment duration are still debated. **Objective:** In this study, we aimed to investigate the clinical effects of omalizumab discontinuation after 5 years of treatment in patients with omalizumab super-responders, the persistence of response and to compare the features of patients, whose symptoms are still well controlled and those who relapsed and re-treated with omalizumab. **Methods:** Clinical and laboratory data of 100 adult patients diagnosed with allergic severe asthma and treated with omalizumab between 2008 and 2020 were evaluated retrospectively. Demographic, clinical, functional, and laboratory parameters of the patients who were re-treated with omalizumab and those who did not need to be re-treated were compared. **Results:** There were 14 super-responder patients, who were treated with omalizumab for 5 years, and the treatment was discontinued then. Omalizumab was not restarted in 9 patients (64%) and was restarted in 5 (36%) patients. No significant difference was presented between these

two groups in terms of demographic, clinical, functional, and laboratory parameters. The baseline total IgE levels of patients, who were re-treated with omalizumab, was found to be higher than those who were not, but this difference was not statistically significant (440 [229–864] IU/mL vs. 164 [85–293] IU/mL; $p = 0.053$, respectively). **Conclusion:** One of 3 patients was re-treated with omalizumab due to loss of asthma control after discontinuation of the treatment. Therefore, omalizumab's immunomodulatory effect may seem to persist in a majority of cases after discontinuation. Also, higher baseline total IgE levels might help to predict the cases that need re-treatment after discontinuation.

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Introduction

Asthma is a common chronic respiratory disease affecting 1–18% of the population, characterized by a variety of respiratory symptoms and expiratory airflow limitation. Severe asthma is defined as the disease that remains uncontrolled despite optimized treatment with high-dose inhaled corticosteroids (ICSs), long-acting be-

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ta-agonists, or requires a high-dose ICS-long-acting beta-agonists combination [1]. In patients with severe asthma, some phenotype-based treatments have become available in recent years. Omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody, is the first biologic therapy approved by the US Food and Drug Administration and European Medicine Agency for the treatment of allergic severe asthma phenotype in patients, who demonstrate sensitivity to perennial aeroallergens and are >6 years of age [2]. In clinical trials and real-life studies, omalizumab has been shown to prevent exacerbations and improve symptoms and quality of life [3–8].

Although omalizumab has been in clinical use since 2003 and there are many studies presented its effectiveness, there is no clear consensus about the optimal treatment duration, and data on whether it has a lasting or resolving effect are lacking. Studies claim that improvement in asthmatic symptoms continues after omalizumab treatment is discontinued and show that these effects are reversible [9–11]. Studies evaluating the rates of re-treating with omalizumab in patients who respond well to omalizumab and whose treatment has been discontinued and studies on markers that can predict this situation are extremely limited.

In our study, we aimed to investigate the clinical effects of omalizumab discontinuation after 5 years of treatment and persistence of response in patients with severe asthma and to compare the features of patients whose symptoms are still well controlled and those who were re-treated with omalizumab due to loss of asthma control. We also aimed to share our clinic's 12 years of omalizumab experience in allergic severe asthma.

Methods

Clinical and laboratory data of 100 adult patients diagnosed with allergic severe asthma according to the Global Initiative for Asthma (GINA) severe and difficult-to-treat asthma guideline [12] and treated with omalizumab for at least 6 months in our clinic between 2008 and 2020 were retrospectively evaluated. Omalizumab is reimbursed by the social insurance institutions of Turkey under these conditions: patients aged 12 years and older with severe persistent allergic asthma and body weight of 20–150 kg, sensitivity to perennial allergens (with skin test or specific IgE positivity), and serum total IgE level of 30–1,500 IU/mL.

Age, gender, asthma characteristics (atopy, the presence of nasal polyps, and nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease) were collected from the patient charts. In addition, the baseline, end of 5 years, and last follow-up results for the following variables were noted: all asthma medications, symptom control measures, blood eosinophil counts, serum total IgE levels, forced expiratory volume in 1 s (FEV₁) values, and the number of

exacerbations that required systemic corticosteroids (SCSs) for at least 3 days within the last year. ICS and SCS were presented as their budesonide and methyl-prednisolone equivalents, respectively.

Symptomatic control was assessed by the GINA symptom control tool (categorical classification): the frequency of daytime symptoms, night waking, reliever treatment use, and activity limitation in the past 4 weeks were questioned at each follow-up [1]. To establish the effect of omalizumab on disease prognosis more efficiently, baseline and the last measures of symptom scores, laboratory and FEV₁ parameters were obtained from the patients' exacerbation-free periods. Total IgE levels were measured by the nephelometric method (Siemens Dade Behring Marburg GmbH, Marburg, Germany). Academic and Ethical Committee approvals were obtained for the study, and due to the retrospective nature of the study, no informed consent was obtained.

Definitions

Asthma exacerbations: An exacerbation was defined as worsening asthma symptoms requiring oral corticosteroids at least 3 days a week or increasing the maintenance oral corticosteroid dose.

Super-responder: Patients who had no asthma exacerbations, systemic steroid use, and well controlled according to GINA categoric symptom classification after at least 12 months were identified as super-responders.

Omalizumab discontinuation: Omalizumab was discontinued in patients who were treated for 5 years. The reason for discontinuation at the fifth year is that recurrence risk increases if it is terminated earlier [13, 14]. Omalizumab was discontinued by fulfilling the criteria:

1. if the patient had no exacerbation history in the last year under omalizumab treatment
2. no need for regular use of systemic steroids
3. well-controlled asthma according to GINA categoric symptom classification (no day or night symptoms, no need for rescuers, and no physical activity limitation as asthma control)

Omalizumab re-treatment: Clinical deterioration was detected by changes in GINA symptom scores and the presence of one or more severe asthma exacerbations. Omalizumab was restarted in patients with frequent exacerbations and uncontrolled symptoms according to GINA categoric symptom classification after discontinuation, and this group is called the "relapsed" group.

The flowchart of the patients included in the study according to the definitions above is shown in Figure 1. Patients who were super-responders and whose omalizumab treatment was discontinued at the end of 5 years were evaluated in the study. The baseline clinical, functional, and laboratory characteristics of those whose asthma control was deteriorated and omalizumab was restarted in the follow-up were compared with those whose asthma control did not deteriorate.

Statistical Analysis

Data recording and statistical analyses were performed using SPSS v22.0 (SPSS Inc., Chicago, IL, USA). The distribution of the data was established using the Kolmogorov-Smirnov test. Numerical data were expressed as mean ± standard deviation or median (25–75th percentile), according to the distribution of the variable. Wilcoxon or paired sample *t* test was performed to test the difference between pre and posttreatment, as appropriate. A *p* value of <0.05 was considered significant.

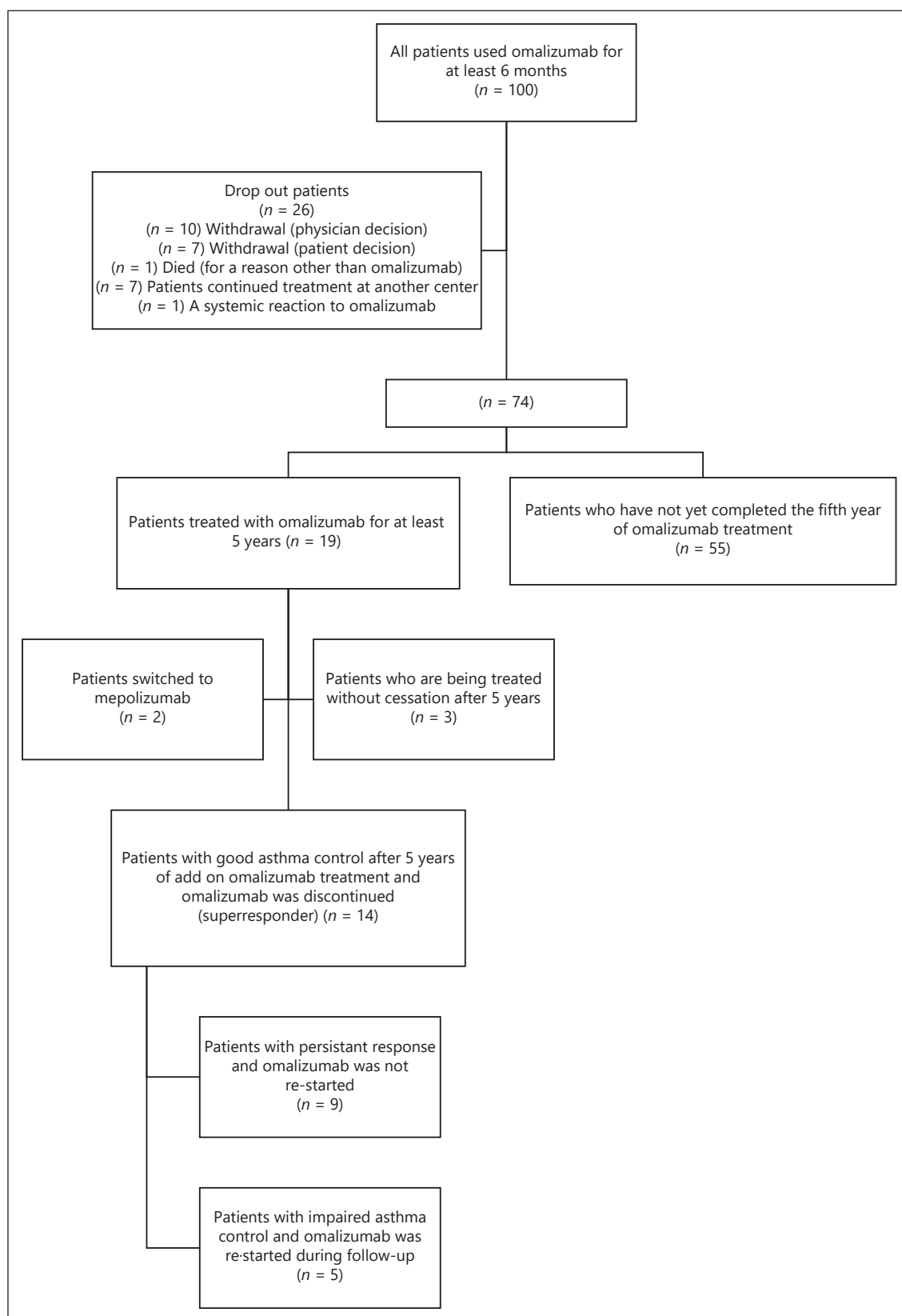


Fig. 1. Patient's follow-up flowchart.

Table 1. Patient characteristics and clinical findings at baseline of who have used omalizumab for at least 6 months

	N = 100
Age, years $\pm$ SD	49.8 $\pm$ 13.1
Female gender, n (%)	79 (79)
Median serum total IgE, IU/mL (IQR)	175 (97.2–426)
Median serum eosinophil count, cells/mL (IQR)	320 (150–615)
Upper respiratory tract involvement, n (%)	
None	10 (10)
Chronic rhinitis	78 (78)
NERD	17 (17)
Treatment duration, months $\pm$ SD	45.9 $\pm$ 26
Allergen sensitization status, n (%)	
Mite	85 (85)
Pollen	23 (23)
Dander	7 (7)
Mold	21 (21)
Single allergen sensitization	61 (61)
Current smoker, n (%)	0

SD, standard deviation; NERD, nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease.

Results

The data of 100 patients, who were followed up with severe allergic asthma and were given omalizumab between 2008 and 2020 in our clinic, were analyzed. Patient characteristics are detailed in Table 1. Seventy of the patients in the study were women. The mean age was 49.8 ± 13.1 years. All the patients had at least one perennial allergen sensitization. The median baseline serum IgE level was 175 (97.2–426) IU/mL (IQR), and the median serum eosinophil count was 320 (150–615) cells/mL (IQR) (Table 1).

The baseline mean inhaler steroid dose was $1,042 \pm 386$ μ g. Patients' treatments are summarized in Table 2. In total, 68% of patients, who had the uncontrolled disease before omalizumab treatment, had the well-controlled disease in their last follow-up. The mean number of systemic steroid-requiring exacerbations per year decreased from 7.2 ± 6.9 to 1.5 ± 1.9 , and FEV₁ values increased from $2,165 \pm 872$ to $2,347 \pm 918$ ccs ($p < 0.001$ and $p = 0.002$, respectively). Blood eosinophil count decreased from 320 (150–615) to 205 (120–442) cells/mL ($p = 0.004$) (Table 3).

Twenty-six of our patients, who used omalizumab, dropped out of our follow-up before the treatment was completed. The reasons for dropping out are shown in Figure 1. Fifty-five patients had not completed 5 years of treatment in the study interval. Only 19 people completed 5 years of omalizumab treatment (Fig. 1). In 2 of these 19 patients, omali-

zumab was switched to mepolizumab because the disease was partially controlled and had markers that predicted an excellent response to mepolizumab treatment. Although these patients were initially more suitable for anti-IL5 treatment, omalizumab had to be started since there was no reimbursement of mepolizumab by the social insurance institution of Turkey at that time. Omalizumab was continued without interruption in 3 patients since they had at least one attack in the last year (however, the number of exacerbations decreased compared to before omalizumab, so the treatment was continued). Omalizumab was discontinued in 14 super-responders. Five (35.7%) of the super-responders were re-treated with omalizumab after 15.6 ± 12.4 months. After re-treatment, the drug was well tolerated, and patients were again followed up without exacerbations and complete disease control. These 5 patients received re-treatment for a median of 25 (11.5–46.5) months. During this period, there were no asthma exacerbation, and asthma control was restored. Nine super-responders were followed up for 30.11 ± 11.17 months without any need for re-treatment.

No significant difference was observed in terms of demographic, clinical, and laboratory findings of the patients between the "relapsed" group and the group that did not need re-treatment (Table 4). However, the baseline total IgE levels of the patients in the re-treatment group were higher than those with well controlled ($p = 0.053$). No significant difference was observed between two groups when FEV₁ levels, eosinophil counts, and total IgE levels were compared at baseline and 5th-year follow-ups (Table 4).

Omalizumab was well tolerated in nearly all of our patient population ($n = 100$). Only one systemic reaction was recorded, and treatment was terminated.

Discussion

Our study showed that in allergic severe asthma, prolonged use of omalizumab treatment ended up with a significant decrease in symptom scores, the number of exacerbations, and improvement in FEV₁ values. We also showed that discontinuation of the treatment after 5 years has a lasting effect in 2 of 3 patients without any need for re-treatment.

Although omalizumab has been in clinical use since 2003, no clear consensus exists about the optimal treatment duration yet. Our reason for cessation in 5 years is that recurrence was reported to be more common if terminated earlier [13, 14]. Therefore, at the end of the 5th year of add-on omalizumab, treatment was discontinued in super-responders. In this study, 36% of super-responders had to start over after a mean of 15.6 ± 12.4 months.

Table 2. All controller treatments at baseline and last visit after omalizumab started

	Baseline	Last visit	<i>p</i> value
ICS dose,* $\mu\text{g} \pm \text{SD}$	1,042 $\pm$ 386	866 $\pm$ 366	<0.001
Other controller medications, <i>n</i> (%)			
LABA	100 (100)	95 (95)	0.05
Montelukast	72 (72)	75 (75)	
Theophylline	8 (8)	4 (4)	
LAMA	20 (20)	13 (13)	–
Total dose of long-term SCSs,** mg/day	106 (<i>n</i> = 18)	15 (<i>n</i> = 5)	

ICS, inhaled corticosteroid; SD, standard deviation; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SCS, systemic corticosteroid. * Budesonide equivalent; ** Represented as the sum of all the patients' daily SCSs as a methyl-prednisolone equivalent.

Table 3. Comparison of baseline and last symptom scores, exacerbation rates, FEV₁ values, and eosinophil counts of all patients (*n* = 100)

	Baseline	Last	<i>p</i> value
Symptom scores (GINA)	2.96 $\pm$ 0.2	1.33 $\pm$ 0.59	<0.001
Complete control, <i>n</i> (%)	0	72 (72)	
Partial control, <i>n</i> (%)	4 (4)	20 (20)	
Uncontrolled, <i>n</i> (%)	93 (93)	6 (6)	<0.001
The number of exacerbations that required SCS for at least 3 days within the last 1 year $\pm$ SD	7.2 $\pm$ 6.9	1.5 $\pm$ 1.9	
FEV ₁ , % predicted $\pm$ SD	77.5 $\pm$ 21.9	84.4 $\pm$ 21.5	<0.001
FEV ₁ , cc $\pm$ SD	2,165 $\pm$ 872	2,347 $\pm$ 918	0.002
Median serum eosinophil count, cells/mL $\pm$ SD	320 (150–615)	205 (120–442)	0.004

SCS, systemic corticosteroid; FEV₁, forced expiratory volume in 1 s; SD, standard deviation.

Table 4. Comparison of demographic, clinical, and laboratory data of omalizumab re-treatment and discontinuation groups

	All patients whose treatment was interrupted at the end of the 5th year (<i>n</i> = 14)		
	omalizumab re-treatment (<i>n</i> = 5)	persistence of response after omalizumab cessation (<i>n</i> = 9)	<i>p</i> value
Age, years $\pm$ SD	47 (45–56)	55 (50–63)	0.181
Female gender, <i>n</i> (%)	4 (80)	8 (89)	1
Nasal polyposis, <i>n</i> (%)	1 (20)	2 (22)	1
NERD,* <i>n</i> (%)	1 (20)	0	0.357
Base FEV ₁ , % predicted $\pm$ SD	85 (64–103)	70 (55–96)	0.487
FEV ₁ in the fifth year % predicted $\pm$ SD	76.5 (56.5–93.5)	68 (65–92)	0.825
Base eos cells/mL (IQR)	320 (163–508)	400 (175–590)	0.306
Eos in the fifth year cells/mL (IQR)	190 (75–320)	570 (165–787)	0.127
Base IgE IU/mL (IQR)	440 (229–864)	164 (85–293)	0.053
Inhaled steroid dose reduction	0	3 (33)	0.258
Base number of systemic steroid use in the last 1 year before starting treatment	2 (0.5–3)	2 (0.5–2)	0.63

* NERD, nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease.

This finding, in line with other studies reported in the literature, shows that in patients, who discontinued omalizumab after 5 years, the rate of restarting is less than half of the patients, due to deterioration of asthma control within 3–4 years after discontinuation [10, 14]. The 52-week, randomized, double-blind, placebo-controlled study of XPORT evaluated the persistence of omalizumab response in patients with moderate-to-severe persistent allergic asthma who discontinued omalizumab after prolonged use. Significantly more patients in the omalizumab group (67%) compared to the placebo group (47.7%) had no protocol-defined exacerbations. This suggests that the continuation of omalizumab after long-term therapy results in continued benefit (asthma exacerbation prevention and improvement in symptom control). On the other hand, the percentage of patients without exacerbation in the placebo arm was also found to be relatively high. This suggests the continued efficacy of omalizumab in some patients after discontinuation. In our study, omalizumab was not started in 9 patients who were super-responders at the end of 5 years and whose treatment was discontinued (64%), and it was started again in 5 patients (36%). This supports the continued efficacy of omalizumab, as in the placebo arm of the XPORT trial, even if omalizumab was discontinued. In the XPORT trial, randomization was stratified for ICS use at baseline and the level of asthma control at baseline (well controlled: ACT score >20 vs. not well controlled: ACT score <20), for the omalizumab dosing interval that the subject received at baseline (2 vs. 4 weeks) and for the study site. A hierarchical dynamic randomization scheme was used to achieve approximate overall balance between treatment groups and within each stratum. In our study, patients who were super-responder at the end of 5 years and whose omalizumab treatment was discontinued were included. It should also be taken into account that the methodology of the XPORT trial and the methodology of our study are different.

Can we predict patients with highest potential for retreat of omalizumab, whose omalizumab treatment was discontinued because they are super-responders? When we compared the demographic data and FEV₁ (%), eosinophil, total IgE levels at baseline, 5th year, last follow-up in the relapsed group and the group that did not need re-treatment, we did not find a statistically significant difference. However, the baseline total IgE levels of the patients, who were re-treated with omalizumab, were higher than those who did not need re-treatment ($p = 0.053$). The baseline total IgE level might help to predict the cases that will need re-treatment with omalizumab after discontinuation. More studies and data are needed as a cutoff value

for the total IgE level which cannot be given within the available data. As far as we know, this is the second study comparing adult patients, with severe allergic asthma, who relapsed and restarted omalizumab, and patients whose clinical response persisted after omalizumab was discontinued. In the first study, in which omalizumab was discontinued after 6 years of treatment, loss of asthma control was observed in 12 of 49 patients in the first year of follow-up [10]. This “failure” group was compared with the “success” group, whose asthma control was still maintained. The baseline demographic and clinical features, atopy, chronic rhinosinusitis, nasal polyps, nonsteroidal anti-inflammatory drug intolerance, asthma control test, exacerbation rate, and FEV₁ (%) values before starting omalizumab treatment were not significantly different. However, it was observed that the total IgE level was higher in the “failure” group at the end of 6 years, and there was a faster decrease in the 6th month after it was stopped. Similarly, in our study, no significant difference was found between the two groups in terms of demographic, clinical, and functional characteristics. The pretreatment total IgE level was found to be higher in the group in which omalizumab was restarted. This difference was not due to a methodological reason since total IgE was measured in the same laboratory and measurement method. Total IgE levels at the end of the fifth year could not be compared due to a lack of data. At different times in both studies (pretreatment in our case, visit of cessation in the other study), total IgE elevation was shown as a parameter to be considered for relapse prediction after omalizumab discontinuation in patients, whose asthma was well controlled after long-term omalizumab use. In a study by Vennera et al. [10], where omalizumab discontinuation decision was given by the patient at the end of the sixth year, the authors noted that the lack of total IgE difference in the pretreatment period may be due to their patient selection criteria. On the other hand, our patients were super-responders and discontinued omalizumab at the end of 5 years.

The small number of patients is one of the major limitations of our study. However, although we are the reference clinic in the region and have 12 years of experience in omalizumab treatment for severe allergic asthma, 19 out of 100 patients completed 5 years of omalizumab treatment. Another limitation is the absence of a group that continued omalizumab despite completing 5 years of treatment, with well-controlled asthma symptoms. Thus, a comparison between omalizumab-continued and -discontinued groups could not be made. Considering the cost-effectiveness and the efficacy, in our clinical practice, we choose the strategy of ending omalizumab treatment in patients, with good asthma

control, at the end of 5 years and follow them. There is certainly a need for studies comparing these groups. However, the importance of our study is the comparison of the demographic and clinical characteristics of the patients who relapsed and had to start omalizumab again and those who did not need to restart because of the persistence of response.

In conclusion, there were significant improvements in exacerbation rates, symptom scores, and FEV₁ levels in patients with severe allergic asthma, with omalizumab treatment. After discontinuation in patients with controlled asthma after 5 years, omalizumab was restarted due to clinical worsening in about 1/3 of the patients within 3 years. This suggests that the immunomodulatory effect of omalizumab may continue in some cases after discontinuation. Higher baseline total IgE levels might help to predict the cases that need re-treatment after discontinuation. However, further studies involving larger numbers of patients are needed to identify potential predictors relapse after discontinuation.

Statement of Ethics

Ethics approval was obtained from the Erciyes University Ethics Committee (Date: November 3, 2021 No: 704). This retrospective study fully conformed to the principles of the Declaration of Helsinki. Due to its retrospective nature, the study was exempted from obtaining written informed consent by the Ethics Committee.

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Conflict of Interest Statement

Bahar Arslan, Gül den Paçacı Çetin, and İnci Gülmez report no conflict of interests. Murat Türk reports congress travel support from Novartis. İnsu Yılmaz reports advisory board, speaker fees, and congress travel support from Novartis, GSK, Chiesi.

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Author Contributions

This study was designed, directed, and coordinated by Bahar Arslan and İnsu Yılmaz as the principal investigators. Data collection was performed by Bahar Arslan, Murat Türk, Gül den Paçacı Çetin, İnci Gülmez, and İnsu Yılmaz. Murat Türk and İnsu Yılmaz analyzed the data. The manuscript was written by Bahar Arslan, Gül den Paçacı Çetin, Murat Türk, İnci Gülmez, and İnsu Yılmaz.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.