

Long-Term Omalizumab Treatment: A Multicenter, Real-Life, 5-Year Trial

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Keywords

Anti-IgE · Omalizumab · Effectiveness · Real-life trial · Long-term treatment

Abstract

Background: Omalizumab has demonstrated therapeutic benefits both in controlled clinical trials and real-life studies. However, research concerning the long-term effects and tolerability of omalizumab is needed. The main objective of this study was to evaluate the effectiveness and tolerability of

treatment with omalizumab for up to 5 years. **Methods:** A multicenter, retrospective, chart-based study was carried out to compare documented exacerbations, hospitalizations, systemic steroid requirement, FEV₁, and asthma control test (ACT) results during 1 year prior to omalizumab treatment versus at 1, 3, and 5 years of treatment. Adverse events and reasons for discontinuation were also recorded at each time point. **Results:** Four hundred and sixty-five patients were enrolled in the study. Outcome variables had im-

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proved after the 1st year and were sustained after the 3rd and 5th years of treatment with omalizumab. Omalizumab treatment reduced the asthma exacerbation rate by 71.3% ($p < 0.001$) at 1 year, 64.3% ($p < 0.001$) at 3 years, and 54.8% ($p = 0.002$) at 5 years. The hospitalization rate also decreased; by the 5th year of the treatment no patients were hospitalized. ACT results had also improved significantly: 12 ($p < 0.001$) at 1 year, 12 ($p < 0.001$) at 3 years, and 12 ($p = 0.002$) at 5 years. Overall, 12.7% of patients reported adverse events (most of these were mild-to-moderate) and the overall drop-out rate was 9.0%. **Conclusion:** Omalizumab had a significant effect on asthma outcomes and this effect was maintained over 5 years. The drug was found to be generally safe and treatment compliance was good.

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Introduction

Despite well-defined strategies for the management of asthma, a substantial proportion of asthmatics, and certainly those with severe asthma, remain poorly controlled [1]. A better understanding of asthma pathophysiology has driven the development of biological therapies that target specific molecular pathways in an attempt to maintain better control.

Omalizumab, a humanized anti-immunoglobulin E (IgE) monoclonal antibody, is the first and most studied biological therapy approved for moderate-to-severe allergic asthma that is inadequately controlled with inhaled corticosteroids (ICs) and long-acting β_2 agonists (LABAs) [2, 3]. The clinical efficacy of omalizumab in this group of patients has been well documented in several randomized controlled clinical trials (RCTs) [4–7]. A pooled analysis of data from 7 omalizumab studies, including 5 randomized, double-blind, placebo-controlled studies and 2 randomized open-label studies, demonstrated a significantly reduced rate of asthma exacerbations as well as a marked reduction in the number of unscheduled outpatient visits, emergency department treatments, and hospitalizations for asthma exacerbations [8]. At the level of patients, the benefit of omalizumab is also expressed as an improvement in asthma-related quality of life [9].

RCTs are considered to be the most reliable form of scientific evidence in the hierarchy of evidence for the assessment of any therapeutic intervention, but they exclude patients, clinical characteristics, and variations in care, which can potentially confound outcomes. This runs the risk of missing a beneficial effect of the interven-

tion [10]. Moreover, it is known that RCTs miss the potential to investigate long-term adherence to the treatment, since they closely monitor the patient [10]. Therefore, evidence from RCTs should be combined with that from real-life studies to provide a fuller picture of the efficacy of an intervention's efficacy and patients' adherence to treatment.

Omalizumab real-life studies from different countries were conducted in parallel [11–29]. The results are consistent with the efficacy and safety profile of omalizumab as observed in RCTs. However, the comparative analysis between RCTs and real-life studies highlighted the need for further research, particularly into the long-term effects of omalizumab [30], since most previous real-life studies reflect a clinical observation lasting <2 years in a relatively limited number of patients [11–29].

This study aimed to represent a multicenter, real-life experience regarding the effectiveness of omalizumab over 5 years in a large number of patients with severe allergic asthma.

Material and Methods

Study Design

This was a multicenter, retrospective study that incorporated data generated during assessments and visits, and conducted as per local standard medical practice, in patients receiving omalizumab for uncontrolled, persistent allergic asthma in Turkey.

Allergy and pulmonology centers allowed to initiate omalizumab treatment for uncontrolled allergic-asthma patients, according to Turkish drug reimbursement rules, were invited to participate in the study. Eighteen centers confirmed their participation.

The study protocol was approved by the local Ethics Committee of the Celal Bayar University, and was conducted in compliance with good clinical practice standards and the Declaration of Helsinki.

Electronic or paper-based hospital medical records were used as source documents, and data were collected between September 2014 and March 2015 by investigator site staff. Only available data were recorded, with no specific action taken to collect missing data.

Patients

Severe allergic-asthma patients, aged ≥ 18 years at the initiation of omalizumab and who had received at least 1 dose of omalizumab as part of routine clinical practice before ethics committee approval, were identified by the investigators and included in the study. Omalizumab treatment had been initiated according to the following criteria: severe, persistent allergic asthma (according to the definition stated by the GINA guidelines [3]), poor control of asthmatic disease despite ongoing treatment with high doses of ICs in association with LABAs, total serum IgE between 30 and 1,500 IU/mL, evidence of sensitization by prick test or specific IgE detection (ImmunoCap; Pharmacia Diagnostics AB, Uppsala, Sweden) to at least 1 perennial allergen and suitable according to the dose

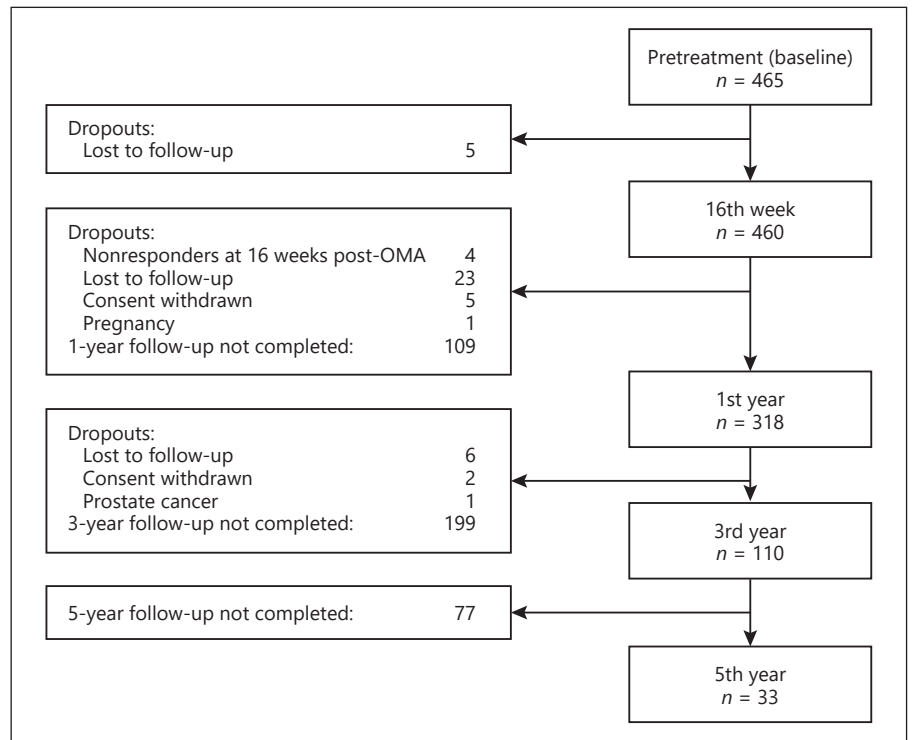


Fig. 1. Patient disposition at the end of year 5 (end of registry). OMA, omalizumab treatment.

table based on the body weight and IgE level. No other inclusion/exclusion criteria were described due to the retrospective nature of the study. However, patients in the participating centers were routinely assessed to exclude an alternative diagnosis which could mimic or accompany severe allergic asthma, such as bronchopulmonary aspergillosis and vasculitides.

Collected Data

Initiation of omalizumab was expressed as the index (baseline) time. Patient demographics and characteristics including medical history (smoking history, disease duration, allergen sensitivity, comorbidities, and concomitant asthma medication), total IgE levels, omalizumab dosage, and frequency were collected at baseline.

Documented exacerbations (defined as an increase in symptoms requiring treatment with systemic corticosteroids, and/or emergency room visits), hospitalizations, and the need for systemic steroid use were collected for 1 year prior to treatment at baseline, and then at 16 weeks and 1, 3, and 5 years of treatment. Lung function test (FEV₁) and ACT results, adverse events, and reasons for discontinuation were also recorded at each time point. The exact time points for assessments could not be stipulated as this was a retrospective study of routine clinical practice.

Effectiveness Measurements

Due to the retrospective nature of the study, we did not define a primary end point. The analysis is descriptive and the effectiveness of the treatment in the patient population observed is defined according to the reduction in exacerbations, hospitalization, and systemic steroid requirement and the improvement in FEV₁ and ACT score.

Response to treatment, as assessed by the physicians' evaluation with the global evaluation of treatment effectiveness (GETE) questionnaire at week 16 and 1, 3, and 5 years of treatment is also noted. GETE is a 5-point scale that rates the response to treatment as "excellent" (complete control of asthma), "good" (a marked improvement), "moderate" (a discernible, but limited improvement), "poor" (no appreciable change), and "worsening." In this study, patients are defined as good responders if the rating of symptoms control is excellent or good, and partial responders if the symptoms control is moderate; poor and worsening correspond to nonresponders [31, 32].

Statistical Analysis

Statistical analysis was performed using the MedCalc v12.7.7 (Ostend, Belgium; <http://www.medcalc.org>; 2013). The normality of continuous variables was investigated by means of the Shapiro-Wilk test.

Descriptive statistics (mean, median, standard deviation, minimum, maximum, and 95% confidence interval for mean) were used for patient demographics and baseline characteristics. Categorical and nominal variables have been tabulated with frequency (*n*) and percentage (%). The percent change in the number of patients who had asthma attacks, asthma-related hospitalizations, and required systemic steroids before and after omalizumab treatment was assessed at 16 weeks and 1, 3, and 5 years of treatment by means of the McNemar test. The difference in mean ACT score, FEV₁ (% of the predicted value [%pred.]) and peak expiratory flow (%) before and after treatment were evaluated by the Friedman test, followed by the Wilcoxon signed-rank test with the Bonferroni correction for post hoc comparison. Statistical significance was accepted when the 2-sided *p* value was <0.05.

Table 1. Baseline demographics and patient characteristics

Age, years	47.7±11.9 (18–82)
Female	353 (75.9)
Male	112 (24.1)
Weight, kg	75 (43–129)
Total IgE, IU/mL	213 (30–1,124)
Duration of asthma, years	13 (1–48)
Smoking history	
Nonsmoker	361 (77.6)
Quitted smoking	49 (10.5)
Still smoking	18 (3.9)
Concomitant allergic disease	
Allergic rhinitis	240 (51.6)
Urticaria	55 (11.8)
Drug allergies	29 (6.2)
Atopic dermatitis	17 (3.7)
Allergen sensitivity	
House dust mite	405 (87.1)
Cat/dog dander	69 (14.8)
Pollen	69 (14.8)
Fungus	66 (14.2)
Cockroach	20 (4.3)

Values are expressed as *n* (%), mean ± SD (range), or median (interquartile range).

Results

Baseline Characteristics:

The files of 465 patients on omalizumab treatment with severe, persistent allergic asthma were eligible for investigation. Among them, 460 patients had finished 16 weeks of omalizumab treatment, and 318, 110, and 33 had completed 1, 3, and 5 years, respectively (Fig. 1).

Baseline demographics and clinical characteristics are shown in Table 1. Mean age was 47.7 ± 11.9 years (range 18–82) and 75.9% of the subjects were women. The median (interquartile range) total IgE level at baseline was 213 (30–1,124) IU/mL and body weight was 75 (43–129) kg. Most of the patients suffered from additional allergic diseases, with allergic rhinitis being the most common. All patients were sensitized to at least 1 perennial antigen including house-dust mites, molds, cat-dog dander, and cockroach (Table 1).

Ninety-four percent (94.8%) of the study population described having at least 1 asthma exacerbation in the year prior to initiating omalizumab and 63.6% had been hospitalized at least once in the previous year. Mean base-

line FEV₁ was 61.2 ± 18.6 (%pred.). Baseline patient questionnaire scores highlighted the poor levels of asthma control. Median (interquartile range) score at baseline for the ACT was 9 (4–24) points (Fig. 2).

Asthma medication (excluding oral corticosteroids) prescribed in the year before omalizumab initiation included ICs and long-acting β₂ agonists for all patients, and leukotriene receptor antagonists for 383 patients (82.4%).

Efficacy Outcomes

The 1st-Year Evaluation

A total of 318 patients completed the first year of omalizumab treatment (Fig. 1). The 94.8 % who had at least 1 asthma exacerbation in the year prior to omalizumab initiation was significantly reduced to 27.2% at 1 year (*p* < 0.001), i.e., a reduction rate of 71.3%. The rate of patients hospitalized at least once due to asthma decreased from 63.6 to 7.2% by the end of the 1st year of treatment (*p* < 0.001), i.e., a reduction rate of 88.7%. Of 53.2% of the patients who had used at least 1 course of systemic steroids in the previous year, the need for steroid use was reduced to 24.8 % at the end of the 1st year (*p* < 0.001), i.e., a reduction rate of 53.4%. The FEV₁ (%pred. ± SD) improved significantly from baseline, i.e., from 61.2 ± 18.6 to 73.8 ± 19.5 at 1 year (*p* < 0.001). Median ACT improved significantly from baseline, i.e., from 9 (4–25) to 21 (5–25) points at 1 year (*p* < 0.001) (Fig. 2).

According to the physicians' evaluation, at the end of the 1st year of omalizumab treatment, there were no non-responders, 303 (95.3%) patients had a good response to omalizumab, and 15 (4.8 %) were partial responders.

The 3rd-Year Evaluation

The records of 110 patients who completed 3 years of omalizumab treatment were evaluated (Fig. 1). Out of 96.3% who described having had an asthma exacerbation in the year prior to omalizumab initiation, this rate was reduced to 34.4% at the end of the 3rd year (*p* < 0.001), i.e., a reduction rate of 64.3%. The rate of patients who were hospitalized and on systemic steroids at least once in the previous year decreased from 58.8 and 66.4% to 3.1 and 19.1% at year 3, respectively (*p* < 0.001), i.e., reduction rates of 94.7 and 71.2%, respectively. FEV₁ (%pred. ± SD) improved significantly, i.e., from 58.8 ± 18.1 at baseline to 75.4 ± 20.1 at 3 years (*p* < 0.001) and the median ACT also improved significantly, i.e., from 9 (4–24) to 21 (8–25) points (*p* < 0.001).

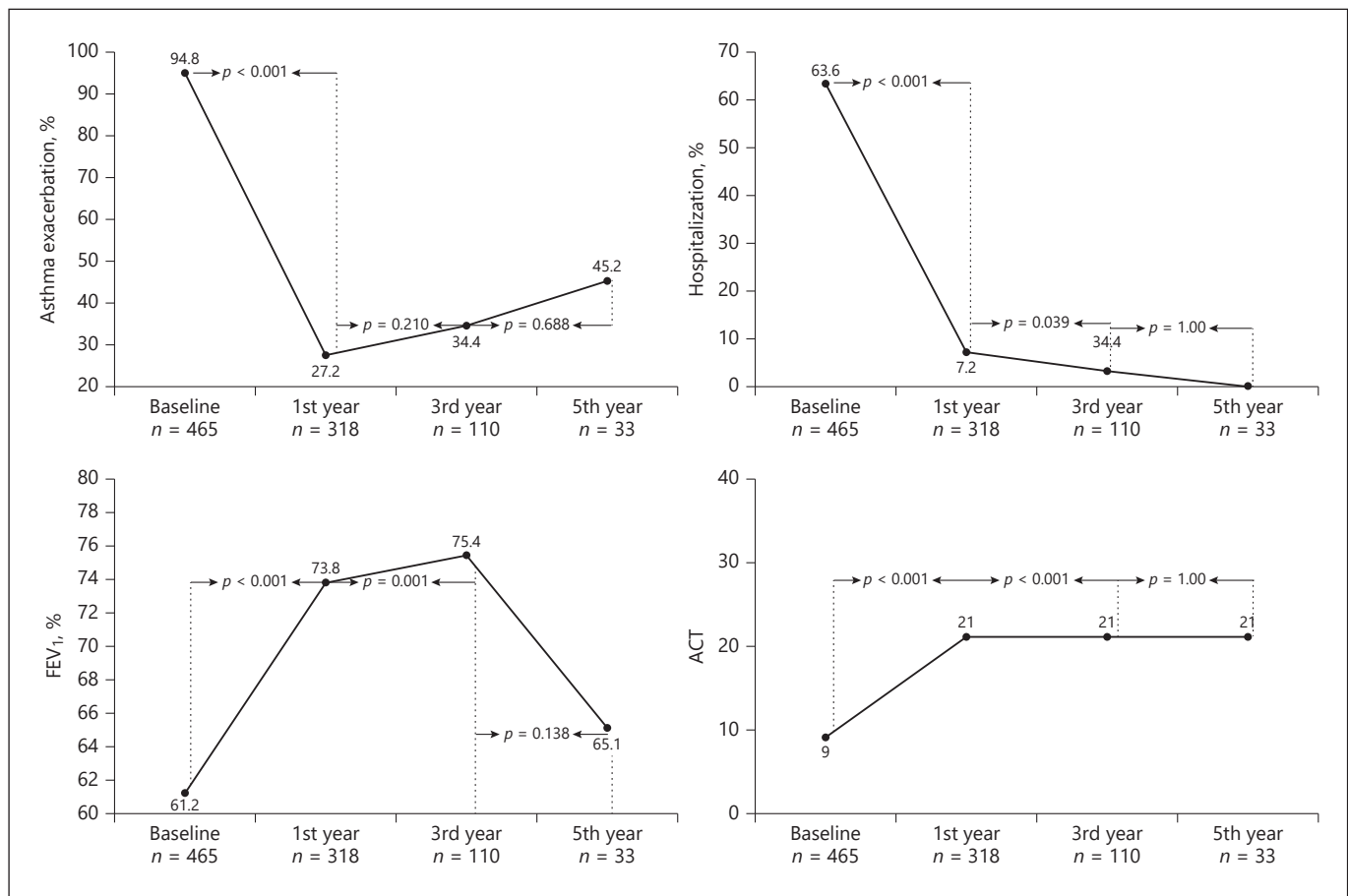


Fig. 2. The value of effectiveness parameters at different time points.

According to the physicians' evaluation at the end of the 3rd year, 103 (93.5%) patients were reported as good responders and 9 (6.4%) as partial responders.

The 5th-Year Evaluation

The records of 33 patients who completed 5 years of omalizumab treatment were evaluated (Fig. 1). The rate of patients with at least 1 asthma exacerbation in the year prior to omalizumab treatment had decreased significantly from 100 to 45.2% ($p = 0.002$), i.e., a reduction rate of 54.8%. At the end of the 5th year of treatment, no patients were hospitalized due to asthma versus a rate of 60.6% at baseline ($p < 0.001$). The ratio of patients who used steroids was reduced from 78.8% at baseline to 30.3% at 5 years ($p < 0.001$). FEV₁ (%pred. $\pm$ SD) improved significantly from 55.9 ± 12.4 at baseline to 65.1 ± 18.5 at 5 years ($p = 0.018$), and median ACT improved significantly from 9 (4–24) to 21 (15–25) points ($p = 0.002$) (Fig. 2).

According to the physicians' evaluation at the end of the 5th year, of 33 subjects, 30 (90.9%) were good responders and 3 (9.1%) were partial responders.

Comparison of the 1st and 3rd Year and the 3rd and 5th Year of Treatment

There was no significant difference in the rate of patients describing at least 1 asthma exacerbation in the 3rd and 1st years of treatment (39.4 vs. 34.4%; $p > 0.05$), but there were further reductions in the rate of patients hospitalized due to asthma (10.3 vs. 3.1%; $p = 0.021$) and treated with a course of systemic steroid treatment at least once (34.5 vs. 19.1%; $p < 0.001$). ACT continued to improve from the 1st to the 3rd year ($p < 0.001$), and FEV₁ (%pred.) underwent a further improvement from 71.8 to 75.4 ($p = 0.001$) (Fig. 2).

The efficacy of the omalizumab treatment was sustained in the 5th year of treatment, with the rate of pa-

Table 2. Dropout rate and reasons for discontinuation

	Baseline to 16 weeks	16 weeks to 1 year	1–3 years	3–5 years
Lack of efficacy		4 (0.9)		Doctor's decision
Adverse events			1 ^a (0.2)	6 (1.3)
Pregnancy		1 (0.2)		
Lost to follow-up	5 (1.1)	23 (4.9)	6 (1.3)	Treatment nonadherence
Consent withdrawn		5 (1.1)	2 (0.4)	41 (8.8)

Values express *n* (%).

^a Prostatic cancer.

tients describing at least 1 asthma exacerbation or hospitalization being similar to after the 3rd year of treatment ($p > 0.05$). There were also no differences in terms of ACT and FEV₁ between the 3rd and 5th years of treatment ($p > 0.05$) (Fig. 2).

Tolerability and Dropout

Overall, 59 patients (12.7%) reported adverse events, mostly mild-to-moderate ($n = 54$). Severe events were seen in only 5 (1.1%) patients. One patient developed prostate carcinoma during the treatment period, although any association of the development of this tumor and omalizumab therapy is questionable. Other severe events were pneumonia ($n = 1$), a traffic accident ($n = 1$), and myopathia ($n = 2$), also not related to omalizumab therapy.

Omalizumab was discontinued in 42 of 465 (9.0%) patients. The physicians' decision to discontinue treatment was the reason for the dropout in 6 (1.3%) patients and 36 (7.7%) were nonadherent to the treatment (Table 2).

Discussion

This study evaluating national data has revealed that omalizumab had a significant effect on asthma outcomes in real life, and that this effect was maintained over the years. The study has the second-largest number of patients out of real-life studies published in various countries, and it is the only one to present 5-year follow-up data. Another important result is that the compliance with omalizumab treatment was quite high during the 5-year period.

A look at numbers of patients in real-life studies published so far [11–29] reveals that the multicenter “EXpe-

Rience” study had the highest number ($n = 925$) [14]. Our study ($n = 465$) is the second-largest after the “France real-life study” [21] ($n = 767$) of the studies presenting real-life data from a single country, and the only one to present the results of 5 years of follow-up. Previous studies have mostly covered a period of ≤ 3 years [11–23, 25]; 1 other study presents 4-year data [24]. We consider that our study presents long-term data with an adequate number of patients.

Appropriate evaluation of our efficacy data first requires the comparison of our study with other real-life studies [11–29]. Regarding demographic characteristics and prestudy clinical status, the real-life studies performed so far have generally included similar patient populations. The patient mean age is generally between 41.3 and 55 years (some have patients > 80 years of age) and most patients are female [30, 33]. We had a similar demographic distribution (mean age 47.7 years and female-to-male ratio 75.9:24.1%). Our rates of allergic rhinitis and smoking history, 2 important factors that could influence disease activity and drug effectiveness, were similar to mean values in the other real-life studies (allergic rhinitis: 51.6 and 69.8%, respectively; nonsmokers: 77.6 and 71.7%, respectively) [30].

Comparison of the disease activity revealed that our patients had similar or even somewhat more severe disease characteristics. The rates of experiencing at least 1 attack in the year before treatment and being hospitalized at least once (94.8 and 63.6%, respectively) were close to the upper limit of the values in (but still within the range of) the other real-life studies (experiencing an attack 88.5–100% and hospitalization 22.4–65.3%). The hospitalization rate was slightly higher in our patient group than the mean upper limit reported in the other real-life studies (3.4 vs. 2.4%) [33]. Taken together, our study eval-

uated a patient group that was similar to previous real-life studies and the effectiveness data we presented are therefore comparable.

We found a statistically significant increase in FEV₁ with omalizumab treatment in this study. This increase was 20, 28.2, and 16.5% for years 1, 3, and 5, respectively. Other real-life studies have also revealed an FEV₁ increase in the patients after treatment (in contrast to RCTs): 7.5% [17] and 25% [24] for year 1. The increase has been reported to be maintained at year 4 as 19% [24, 33]. Although the reason for the difference between FEV₁ results reported from real-life studies and RCTs is not clear, one study emphasized the need for longer treatment to ensure an FEV₁ increase [19] but this has not yet been clarified.

The number of attacks and hospitalizations are important indicators of the use of disease-related health care services. We found a significant decrease in the number of attacks in this study, similar to in previous real-life studies. The rates of decrease were 72, 64, and 55% for years 1, 3, and 5, respectively. Other real-life studies have reported 1st year decrease rates of 45.7% [25] and 80% [13, 15]. There are no studies to directly compare our year 3 and year 5 results, but the closest are a year 2 result of 73.2% [27] and a year 4 result of 70% [24].

Similar to the decrease in the number of attacks, we found a significant decrease in the hospitalization rates with omalizumab treatment. The decrease in hospitalization rate was 89% and 95% in years 1 and 3, respectively. There was no hospitalization of any of the patients who completed the 5th year of the treatment. Previous studies reported a hospitalization decrease within the range of 50 [26] to 96% [13] in the 1st year, and the only other study with 3-year data on subjects reported a decrease of 94.5% [27].

The main reason for the significant decrease in yearly attacks and hospitalizations is the marked improvement of asthma symptom control. The median ACT score before omalizumab use was 9 but this increased markedly after the first year (median ACT 21). Real-life studies also evaluated the day-and-night symptoms ratio directly [12, 25], in addition to using questionnaires such as the ACT [15, 24, 25, 27] and the Asthma Control Questionnaire [18, 28] to evaluate asthma symptom control. The general result of these studies is a marked decrease in symptoms and an improvement in the relevant scores, similar to in our study.

Another result of our study is that omalizumab treatment efficacy was maintained over the years, or even increased (Fig. 2). The optimal duration of omalizumab

treatment has not been clearly identified [34, 35]. However, a previous study emphasized the need for long-term use for the potential effects to develop and a need for relevant data [19]. We therefore believe our results will provide an important reference regarding this approach.

The 5-year follow-up data of our study have enabled the evaluation of both effectiveness and long-term treatment compliance. The study dropout rate in the 5-year period has been acceptable at 9%. Only 7.7% of the patients did not adhere to the treatment. We observed that nonadherence was more common in the early period, and that compliance increased over time (6% for 16 weeks to 1 year, 1.7% for 1–3 years, and 0% for 3–5 years) (Table 2). This is probably due to the efficacy of the medication and its continuing effectiveness through the years. Although a general consensus about the definition of “acceptable adherence” has not been reached, a rate >80% has been considered satisfactory [29, 36]. Some real-life studies also reported the dropout rate. In several [16, 19, 24, 36], all patients continued treatment, and discontinuation due to the patients’ decision was in the range of 1.4–8.4% in others [11–15, 17, 22, 36].

An important limitation of our study is that it is chart-based and retrospective. We therefore focused on using the criteria: number of attacks and hospitalizations, and ACT and FEV₁ values to evaluate effectiveness, as these could all be clearly recorded in this retrospective study. Although the charts were evaluated retrospectively, the values were recorded prospectively. We therefore feel that the retrospective collection of the data has not resulted in any deterioration of their quality. However, we were unable to collect accurate data on the steroid doses and other medications, and have therefore not commented on these.

The retrospective nature of the study may have reduced the accuracy of the safety data. The recording of side effects in real life is usually up to the physician’s initiative within the limits of legal responsibility, and is not as rigid (with defined limits) as in RCTs. However, we could say this is a common problem in observational studies. A review of real-life omalizumab studies shows that side effects have been reported in a very wide range, from a very low (2.7% for 2 years) [15] similar to our results (12.6% for 5 years) to a very high (55.6% for 1 year) rate [22, 33]. This could be explained by the more detailed recording of side effects in early studies compared to later studies where the effectiveness and safety of omalizumab were emphasized [33]. Most (54/59) of the side effects in our study were reported as mild-to-mod-

erate in severity. None of the severe side effects were thought to be due to omalizumab, and the drug was only discontinued in 1 patient. Despite the retrospective nature of our study, our data indicate that omalizumab use is safe in the long term.

In conclusion, our study with 5-year data and a large patient sample has reinforced the effectiveness and safety of omalizumab reported by previous studies, and revealed that the efficacy is maintained (with some increase over time). We have also shown that adherence to omalizumab treatment is good and does not decrease over the years.

Disclosure Statement

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