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PHARMACOTHERAPY

Assessment of Long-term Omalizumab Treatment in Patients with Severe Allergic Asthma Long-term Omalizumab Treatment in Severe Asthma

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Objective. Several clinical studies have demonstrated the effectiveness of omalizumab in patients with severe allergic asthma but the treatment period has always been relatively short (4–12 months). In the literature, there are a few data about the long-term omalizumab therapy. We aimed to assess the long-term clinical and functional effectiveness of omalizumab treatment in severe allergic asthmatic patients, *Methods.* Medical records describing the patients' status before the start of treatment, and also having been registered at the end of 4th, 12th, and 36th months from the commencement of treatment, and at the last visit where the patient was evaluated were used for omalizumab effectiveness assessments. Twenty-six patients (female/male: 21/5) with severe allergic asthma, uncontrolled despite GINA 2006 Step 4 therapy, were included in the study. Effectiveness outcomes included spirometry measurements, level of asthma control measured by asthma control test (ACT), systemic glucocorticosteroid (sGCS) use, emergency room (ER) visits, and hospitalizations for severe exacerbations. In addition, the quality of life was assessed using the quality of life questionnaire AQLQ(S) before, 4, and 36 months after treatment, *Results*. The mean age was 47.6 ± 13.9 and duration of allergic asthma was 22.7 ± 10.1 years. Serum total IgE levels were 322.0 ± 178.1 IU/mL. Mean duration of omalizumab treatment was 40.81 ± 8.2 months. FEV_1 improved significantly at all control points versus baseline ($p < .05$). The level of asthma control as evaluated by ACT improved significantly after treatment ($p < .05$). We determined significantly reduced numbers of exacerbation, emergency visits, hospitalizations, sGCS, and SABA use by the end of 36 months ($p < .05$). The proportion of patients with improvements larger than 1.5 points in AQLQ(S) total score was 80.7% at the 4th month and 96.1% at the 36th month of treatment, *Conclusions*. This study showed that long-term therapy with omalizumab for up to 3 years was well tolerated with significant improvement both in symptoms and lung functions. Accordingly, long-term omalizumab treatment may be recommended for responders.

Keywords anti-IgE, asthma control test, omalizumab, quality of life, severe asthma

INTRODUCTION

Uncontrolled asthma is a condition associated with high morbidity and healthcare costs, both in our country and worldwide, despite all the advances in the pathogenesis, diagnosis, and treatment of the disease. While it is possible to control the disease in patients with mild to moderate asthma with available anti-inflammatory treatments in most of the cases, it is known that the condition may not be adequately controlled in some of the patients with severe persistent asthma despite maximal therapy (1). Inadequate control in asthma has significant consequences including increased morbidity and mortality, decreased quality of life, and increased healthcare costs (1–4).

Omalizumab (Anti-IgE), a humanized monoclonal antibody developed against IgE, binds to the circulating free IgE, preventing it from binding to high- and low-affinity receptors. It thus reduces the amount of free IgE which would trigger the allergic inflammatory pathway. Omalizumab is a new treatment choice which may be added to inhaled corticosteroids (ICS) and the long-acting β_2-agonist (LABA) therapy for uncontrolled patients with severe, persistent allergic asthma (5–7). The effectiveness and safety profile of Omalizumab therapy in severe allergic asthma patients has been established by several randomized clinical trials (5–9). Omalizumab, which received approval in 2003 in the world and in 2008 in Turkey, is now listed in the national and international asthma guidelines.

There is a well-established relationship between increased frequency of asthma attacks, hospitalizations, need for rescue medication and corticosteroid use, and an increased morbidity and mortality in patients with uncontrolled severe persistent asthma. On the other hand, the importance of assessing the patients' quality of life and the awareness regarding this subject is gradually increasing. Favorable effects on asthma exacerbations, hospitalizations, corticosteroid use, and quality of life have been demonstrated both in clinical studies with selected patients and in real-life studies, although treatment periods in most of these studies were as short as 4–12 months (9–15). We are well aware from the literature that there are only a few studies on the long-term effectiveness and quality of life with omalizumab treatment in severe asthmatic patients (16–21). These studies are summarized in Table 1.

Because the value of short-term treatment outcomes is relatively limited, assessments for longer periods of treatment are required. The present study evaluated the clinical and functional effectiveness, effects on quality of life, and the continuity of omalizumab treatment for durations of 3 years and longer in patients with severe allergic asthma.

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TABLE 1.—Effectiveness of long-term omalizumab treatment demonstrated in randomized controlled trials and long-term "real-life" studies.

Study and publication year	Study design	Number of patients, treatment period and age±SD (year)	Effectiveness outcomes	Assessment point	Results
Pace et al., Italy 2011 (16)	Part of a prospective clinical trial (CIGE0250011), retrospective	7 patients 7 years 50 ± 8	FEV_1, Symptom score number of exacerbations, use of antibiotics, additional asthma medications (systemic steroids and bronchodilators)	Baseline, 4 years, 7years	-increased FEV_1, -reduced symptom score, -reduced number of severe exacerbations, -reduced number of nebulized corticosteroids, bronchodilators cycles, antibiotic therapy cycles and oral corticosteroids cycles and oral corticosteroids cycles
Menzella et al., Italy 2012 (20)	Part of a prospective clinical trial (CIGE025A2425), retrospective	11 patients 4 years 47.5 ± 9.6	FEV_1, number of exacerbations, AQLQ, GETE, cost analysis	Baseline, 32 weeks, 4 years	-increased FEV_1, -reduced number of severe exacerbations, -good/excellent response GETE- -reduced use of oral corticosteroids -reduction in healthcare costs
Storms et al., U.S.A., 2012 (18)	Retrospective, real-life experience	52 patients 3 years ↑ (13 patients 6 years) 52 (14–82)	FEV_1, number of exacerbations, ACT, rescue medication use	Baseline, 1year, 3 years, 6 years	-non-significantly increased FEV_1 (at 3 years), -reduced number of severe exacerbations, -decreased number of used bursts systemic corticosteroids -increased ACT- -reduced rescue medication use
Tzortzaki et al., The South-Eastern Mediterranean 2012 (17)	Retrospective, real-life experience, multicentre	60 patients 4 years 54 ± 14	FEV_1, number of exacerbations, ACT, additional asthma medication	Baseline, 4 months, 1 year, 4 years	- increased FEV_1, -reduced number of severe exacerbations, -increased ACT -the used of inhaled steroids decreased
Dal Negro et al., Italy, 2012 (21)	Prospective study	16 patients 3 years 45.4 (31–64) (min–max)	FEV_1, number of exacerbations, IgE levels, ACT, SGRQ, cost analysis	Baseline, 6 months, 1 years, 18 months, 2 years, 30 months, 3 years,	-increased FEV_1, -reduced number of severe exacerbations, -improve asthma control, -improve quality of life, -reduction in symptomatic drug and hospital care costs

Notes: ACT—Asthma control test; AQLQ(S) = Asthma quality of life questionnaire; GETE = The global evaluation of treatment effectiveness scale; Severe exacerbations were defined by the presence of symptoms at rest requiring systemic corticosteroids or admission to emergency services or hospitalization.

MATERIALS AND METHOD

Patient Population

This was a retrospective observational study and evaluated 26 severe allergic asthma patients who received Omalizumab therapy for 3 years or longer at the Department of Chest Diseases of our university between 2006 and 2012. Five patients were initially enrolled as part of the CIGE025A2425 international multicentre, open-label, parallel-group clinical trial (November 2005/ September 2008). The study protocol was approved by the local Ethical Committee.

The diagnosis of asthma in all patients was made according to GINA 2006 criteria. Briefly, the patients had to have a clinical history of symptoms compatible with asthma and reversibility of the obstruction had to be determined by spirometry (postbronchodilator test with change of $FEV_1 \geq 12\%$ and $\geq$200ml) (22).

Omalizumab treatment was initiated in the participating subjects based on the following criteria:

(1) diagnosed with asthma
(2) older than 12 years of age
(3) serum total IgE levels of 30–700 IU/ml
(4) perennial allergy established by skin test and/or specific IgE
(5) uncontrolled severe persistent asthma despite regular high-dose treatment with ICS + LABA
(6) suitable according to the dose table based on the body weight and IgE levels

Treatment was continued if the patient responded to therapy in accordance with the scientific criteria with Omalizumab at 16 weeks. Patients for whom Omalizumab treatment was initiated and who received treatment for 3 years and longer were evaluated.

Omalizumab Treatment and Accompanying Asthma Medications

The patients' omalizumab doses were determined from the Omalizumab dose table according to their baseline body weight and total IgE levels. Omalizumab was administered regularly every 2 or 4 weeks by subcutaneous injection based on the dose table. The patients were monitored at the clinic for two hours following injections against the risk of developing reactions. No restrictions were made for ICS, LABA, or other asthma medications during the treatment period.

Data Collection and Assessment of Treatment Effectiveness

Medical records taken before the start of treatment, at the 4th, 12th, 24th, and 36th months from the beginning of the treatment and at the last visit where the patient was evaluated were reviewed to evaluate the effectiveness of omalizumab therapy. Treatment effectiveness was evaluated with the parameters of respiratory function tests, asthma control level, short-acting β2-agonist use, systemic glucocorticosteroid (sGCS) use, severe episode frequency, number of emergency room visits, and hospitalizations.

Asthma attacks requiring systemic corticosteroids or hospitalization were considered as severe asthma episodes.

The average number of attacks, emergency room visits, and hospitalizations during the past one year before the start of omalizumab treatment were recovered from hospital records and were recorded as baseline values.

Asthma control levels were assessed using the Asthma Control Test (ACT). The ACT is a 5-item questionnaire evaluating the previous 4 weeks. A total score of 25 indicates complete control, scores between 20–24 indicate partial control, and scores lower than 19 indicate uncontrolled patients (23).

In addition, patients' quality of life was evaluated by using the AQLQ(S) quality of life questionnaire before the treatment and by the end of the 4th and 36th months of therapy. The AQLQ(S) is a health-related quality of life questionnaire consisting of 32 items. The items are in four domains: symptoms (12), activity limitations (11), environmental stimuli (4), and emotional function (5). Patients recall their experiences during the previous 2 weeks and score each item on a 7-point scale where a higher score corresponds to a better quality of life. Each participant completed the self-administered, Turkish language version of this instrument in this study. Changes in the score when assessed at two different time points should be at least 0.5 in order that the change may be considered "minimal important". Changes in the quality of life scores higher than 1 are considered moderate and changes higher than 1.5 are considered excellent (24, 25).

Statistical Analysis

Descriptive statistics were presented as mean $\pm$ standard deviation (SD), median, and *n* (%).

The paired *t*-test and Wilcoxon paired test were used for comparing the main clinical and functional parameters before and after omalizumab therapy. SPSS (Statistical package for Social Sciences, for Windows Release 16.0, California, USA) package software was used for statistical analyses. Statistical significance was set at $p < .05$.

RESULTS

Patients' Demographical Data and Functional Assessments

In our clinic, a total of 26 patients received Omalizumab treatment for more than 3 years between 2006 and 2012. The mean duration of omalizumab treatment was 40.81 $\pm$ 8.2 months. The patients' demographical and clinical data are presented in Table 2.

Mean baseline FEV_1 value was 48.4 $\pm$ 10.4. The patients' FEV_1 values improved markedly at year 1 compared to baseline and this improvement was maintained for 3 years and during subsequent follow-ups

TABLE 2.—Demographic, clinical, and spirometric data of the patients.

Sex (F/M)	21/5
Age (years)	47.6 ± 13.9
Body Weight (kg)	70.6 ± 10.9
Duration of allergic asthma (year)	22.7 ± 10.1
Prick test	(*n*)
House dust mites	20
House dust mites + another inhaled allergen	5
Another inhaled allergen	1
*Mean duration of omalizumab treatment (months)	40.81 ± 8.2 (36–62)
Total IgE (IU/mL)	322 ± 178.1
Baseline FEV_1 (% pred.)	48.4 ± 10.4
Mean dose of ICS (fluticasone equivalent/day)	1034.21 ± 169.2
Rescue medication use (puffs per day of SABA)	8.46 ± 2.25
Oral CS use, n (%)	6 (23.1)
Leukotriene antagonists use, n (%)	16 (61.5)

Notes: Data are expressed as mean ± SD; * mean ± SD (min–max). Abbreviations: FEV_1—forced expiratory volume in the first second; ICS—inhaled corticosteroids; SABA—short acting β2-agonists.

[(ΔFEV_1 = + 24.5 ($p < .05$) at month 12; ΔFEV_1 = + 21,5 ($p < .05$) at month 24; ΔFEV_1 = + 23 ($p < .05$) at month 36 and ΔFEV_1 = + 20,4 ($p < .05$) at the last visit where the patient was evaluated] (Figure 1).

Systemic steroid therapies used in six patients at the start of omalizumab treatment, had been discontinued after one year. The patients did not require recommencement of systemic steroid treatment after 3 years and subsequent follow-ups.

The ratio of the patients using beta 2-agonists when necessitated is given in "Figure 2". Rescue medication need decreased significantly after 1 year of treatment with omalizumab and this improvement was maintained for 3 years and beyond (decreases of 75.3% after 1 year, 83.5% after 2 years, 78.8% after 3 years, and 81.2% at the last visit where the patient was evaluated were observed).

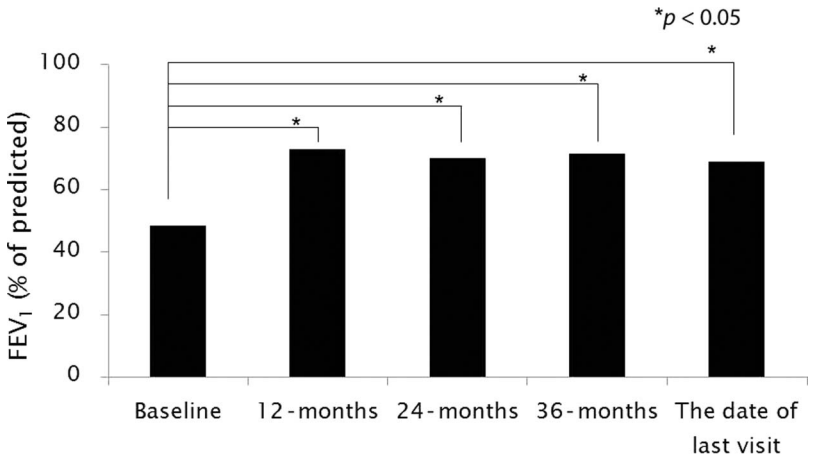

FIGURE 1.—Effectiveness of omalizumab treatment on FEV_1. Twenty-six severe allergic asthmatic patients were treated with omalizumab for up to 62 months. The FEV_1 at baseline and follow-up of patients was assessed. FEV_1 improved statistically significantly at all time points versus baseline ($p < .05$).

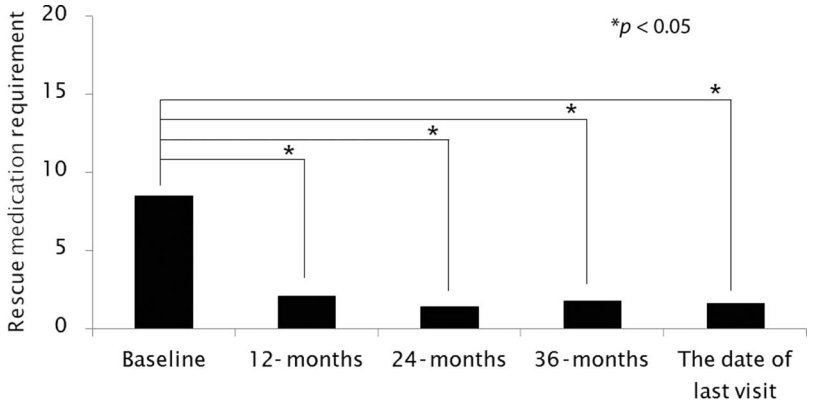

FIGURE 2.—Rescue medication requirement in different time points. Twenty-six severe allergic asthmatic patients were treated with omalizumab for up to 62 months. Rescue medication requirement was reduced during the follow-up period of omalizumab treatment versus baseline (all *p*-values <.05).

Effectiveness of Omalizumab Treatment on Asthma Control

Asthma control level assessed by ACT improved significantly at the 12th month after the commencement of treatment versus baseline (+Δ8.8, $p = 0.001$), which was maintained at 24th month (+Δ10.3, $p = 0.001$), 36th month (+Δ11.6, $p = 0.001$) and at the last visit where the patient was evaluated (+Δ11, $p = 0.001$)and at the last visit where the patient was evaluated (+Δ11, $p = 0.001$) (Figure 3). Comparison of patients' mean data for the 12-month period before Omalizumab treatment and the data at the end of the 12th month of treatment demonstrated a 90% reduction in the number of exacerbations, 93.3% decrease in the number of emergency room visits and a 71.3% decrease in the number of hospitalizations. This improvement was maintained for 3 years and beyond ($p < 0.05$) (Figure 4).

Effectiveness of Omalizumab Treatment on Asthma Attacks, Emergency Hospital Admissions, and Hospitalizations

Comparison of patients' mean data for the 12-month period before Omalizumab treatment and the data at the end of the 12th month of treatment demonstrated a 90% reduction in the number of exacerbations, 93.3% decrease in the number of emergency room visits, and a 71.3% decrease in the number of hospitalizations. This improvement was maintained for 3 years and beyond ($p < .05$).

Effectiveness of Omalizumab Treatment on Quality of Life

Patients' scores from quality of life questionnaire AQLQ(S) before the start of treatment and at 4th and 36th months after the commencement of treatment are listed in Table 3.

Relative improvements in AQLQ(S) total scores at months 4 and 36 with treatment are demonstrated in Table 4. At least a 0.5-point score increase was considered as minimal important and it was observed in a total of 26 patients, of whom 20 had excellent improvements (>1.5 point) in quality of life total scores after 4 months. Assessment at the end of 3 years demonstrated that this improvement was maintained with further gradual increases in quality of life scores.

Tolerability of Omalizumab Treatment and Adverse Effects

No significant systemic adverse effect was observed in any of the patients throughout the study and the treatment was well tolerated by the patients. Only one patient (3.8% had a moderate local reaction at the injection site at the 32nd month of treatment.

TABLE 3.—Health-related quality of life scores of asthma patients before and after omalizumab treatment.

	Baseline	4 months	36 months
AQLQ(S) symptoms	2.45 (2–3.08)	5.49 (4.25–6.16)	6.12 (5.66–6.45)
AQLQ(S) activity	1.81 (1.49–2.83)	4.36 (4.15–5.02)	5.22 (4.97–5.74)
AQLQ(S) environment	1.5 (1.25–1.5)	2.87 (2–3.5)	3.25 (2.75–4)
AQLQ(S) emotions	1.80 (1.20–2.65)	4.3 (3.15–5.05)	5.40 (4.30–5.65)
AQLQ(S) total	1.98 (1.62–2.88)	4.52 (3.83–5.19)	5.34 (5.08–5.46)

Notes: Data are expressed as median (25th percentile–75th percentile[P_{25}–P_{75}]). AQLQ(S)—Standardized Asthma Quality-of Life Questionnaire.

DISCUSSION

The present study evaluated the effectiveness of long-term omalizumab treatment in severe allergic asthma patients who received omalizumab treatment for 3 years or longer in our healthcare centre. Significant reductions in the number of attacks, emergency room visits and hospitalizations, sGCS, and SABA beginning from the 4th month compared to baseline as well as significant improvements in pulmonary functions, asthma control, and quality of life were observed and these improvements were maintained for 3 years and longer during which the patients stayed on treatment.

The most important aspect of the study was that it presents real-life data in Turkey on the effectiveness of omalizumab treatment in the long term (3 years and beyond). The majority of the previous real-life omalizumab studies with asthmatic patients had treatment durations as short as 4–12 months and the data on long-term effectiveness is quite limited. These short–term real-life studies show that omalizumab treatment is effective in reducing the number of asthma exacerbations, improvement of quality of life, reducing symptom severity, and improvement of asthma control (9–15). An earlier real-life omalizumab study by Baybek et al. from Ankara evaluated the effectiveness of omalizumab treatment of 15-month duration and as for the last-time evaluation point where the patients were assessed, reductions in asthma attacks, emergency hospital admissions, and hospitalizations by

TABLE 4.—Effectiveness of omalizumab treatment on health-related quality of life.

	4 months	36 months	*p*-value
Percentage improving in AQLQ total score >0.5	96.15%	100%	>.05
Percentage improving in AQLQ total score >1.5	76.9%	96.15%	.042

Note: AQLQ(S)—Standardized Asthma Quality-of Life Questionnaire.

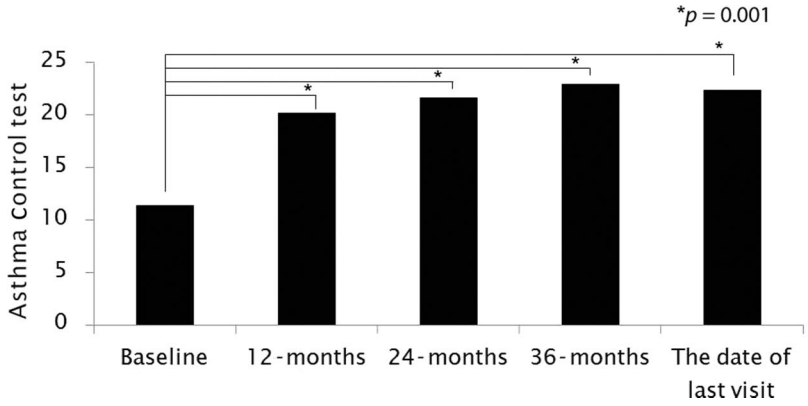

FIGURE 3.—Effectiveness of omalizumab treatment on asthma control evaluated by asthma control test. Twenty-six severe allergic asthmatic patients were treated with omalizumab for up to 62 months. The asthma control tests at baseline and follow-up of patients were assessed. Asthma control test improved statistically significantly at all time points versus baseline ($p = .001$).

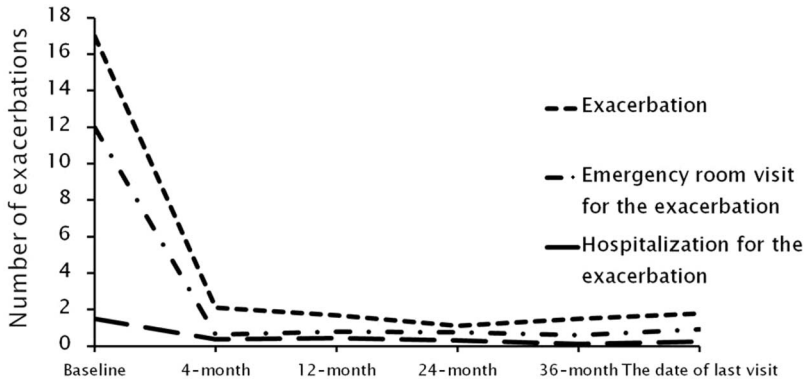

FIGURE 4.—Effectiveness of omalizumab treatment on severe asthma exacerbation rates at different time points. Twenty-six severe allergic asthmatic patients were treated with omalizumab for up to 62 months. Severe exacerbation rates were reduced during the follow-up period of omalizumab treatment versus baseline (all p-values $<.05$).

93, 95, and 86%, respectively, relative to baseline were reported as Turkish data (8). These findings were consistent with the real-life results reported from several European countries.

We aimed to assess the long-term effectiveness of omalizumab together with the evaluation of the data available from previous published studies. Pace et al. evaluated the clinical effectiveness of omalizumab use for the longest period (7 years). However, this study, as a part of a prospective clinical trial, included a very limited number of patients (seven patients). The study reported significant improvements in respiratory function and reductions in symptom scores, number of attacks, and systemic steroid, antibiotic, and inhaler therapy use after 4 and 7 years (16). Another study on long-term omalizumab treatment was a multicenter retrospective south-eastern Mediterranean real-life study involving 60 patients from Greece and Cyprus which reported the results of 4 years of treatment. This study described a significant improvement in respiratory function and asthma control at month 4, as well as significant reductions in the number of asthma attacks and inhaled steroid dose, with improvements achieved at the 4th month maintained at the end of 4 years (17). Storms et al. retrospectively analyzed the data of patients treated at clinics with Omalizumab from the treatment start to month 3 and thereafter annually, using the data covering the period between 2003—when Omalizumab was authorized in the USA—and 2010. Analyses of long-term omalizumab treatments including 3 years for 52 patients and 6 years for 13 patients demonstrated better asthma control improving gradually over years, with reduced symptoms and rescue medication, while FEV_1 levels remained stable (18). Another study which assessed long-term omalizumab treatment was a retrospective study analyzing 4-year treatment results of 11 patients enrolled as a part of a prospective omalizumab study in Italy. This study also reported improved respiratory functions, quality of life, and a marked decrease in the number of severe attacks (94.7%) at the end of 4 years of treatment when compared to baseline data. Unlike other studies, a cost-effectiveness study was also performed which demonstrated a marked decrease in costs associated with hospitalization, emergency room visits, and attack management (20). We retrospectively analyzed the

data of patients who received long-term Omalizumab treatment. Twenty-six patients received the treatment for 3 years and 6 patients for 5 years. A significant improvement in respiratory functions and a marked increase in asthma control, marked reductions in ICS dose and sGCS use, reduction in the need for rescue medication, and significant reductions in the number of asthma attacks, emergency room visits, admissions, and hospitalization have been put forward. Our clinical and functional results revealed similarities with the previously published long-term omalizumab studies.

Short-term omalizumab studies demonstrated that omalizumab treatment resulted in excellent level of improvement in asthma-related quality of life (10, 11, 26, 27), however, there are a few studies investigating the effect of long-term omalizumab treatment on the quality of life. Menzella et al. performed a retrospective evaluation on the 4-year results of 11 patients enrolled as part of a prospective clinical trial and determined significant improvements in all patients, 81.2% of them achieving excellent improvement, at the end of 4 years (20). Dal Negro et al. evaluated the effectiveness of omalizumab treatment in the long term (3 years) and determined a significant and progressive improvement in health-related quality of life (21). Similarly, our study also found a significant improvement in AQLQ(S) total scores at the end of 3 years. The proportion of patients achieving excellent level of improvement was 96.1%, somewhat higher. These results indicate that patients receiving long-term omalizumab treatment achieve improvements in quality of life in addition to improved asthma control, reduced asthma attacks, hospitalizations, rescue medication need, and corticosteroid use.

Available long-term data from studies on the tolerability and adverse effect profile of long-term omalizumab demonstrate that none of the patients had had a serious systemic side effect during the course of treatment and that the treatment was well tolerated (16, 17, 20). Studies by Pace and Menzella did not report any adverse effects, severe or mild, in any of the patients (16, 20). Similarly, in a study by Tzortzaki et al., no serious adverse effects were observed; 11.6% (7) of the patients experienced mild to moderate headache, and 3 patients reported local reactions, and 2 reported arthralgia (17). In our study, no serious adverse event requiring treatment discontinuation was observed. Only one patient (3.8%) had a moderate injection site reaction at month 32 of treatment. This suggested that omalizumab was a safe treatment in the long term also.

The major limitation of our study was the relatively low number of patients. This was mainly associated with the low total number of patients who received omalizumab therapy because of the short period since the approval of the drug in our country. Another reason was that, only the results from a single study were evaluated in this study, although the healthcare facility was among the few centers with patients who used omalizumab for more than 3 years in Turkey. On the other hand, previous studies on real-life experience with omalizumab also had low number of patients. The other limitation was the retrospective design of the study and selection of patients who had favorable initial response (approximately 16 weeks after the first treatment with omalizumab). Because of this selection bias, the patients included in this study might have been more responsive to omalizumab in the long term. Therefore, the long-term benefits of omalizumab treatment cannot be determined for all patients by our study. On the other hand, we would like to remind the reader that the primary purpose of this study was to evaluate the persistency of long-term results provided by omalizumab administered for up to 3 years in severe asthmatic patients who had an initial response to omalizumab and not the long-term benefits in all the patients who were put on omalizumab therapy. The results of this study showed that the clinical and functional effectiveness of omalizumab improve over time, as shown by few studies about the long-term treatment (16, 20).

The major strength of our study was that it reproduced real-life data that confirmed the long-term clinical and functional effectiveness of omalizumab treatment, which was previously demonstrated in selected patient groups in clinical trials with short durations, for example 12 months, and in real-life studies where again the short-term data were reviewed.

Conclusion

The present study demonstrated with real-life data that long-term omalizumab treatment for 3 years and longer results in significant improvement in symptoms and lung functions in our retrospectively selected patient population, was well tolerated by the patients, and produced significant improvement in patients' quality of life. However, a decision for the duration of omalizumab therapy in the long run cannot be achieved with the results of our study and hence further clarification with additional studies should be implemented.

Declaration of Interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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