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RESEARCH ARTICLE

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Omalizumab in Practice: Ten-Year Experience of A Tertiary Referral Allergy Centre

Nida ÖZTOP, Semra DEMİR, Şengül BEYAZ, Özdemir Can TÜZER, Bahauddin ÇOLAKOĞLU, Suna BÜYÜKÖZTÜRK, Aslı GELİNCİK

Department of Internal Medicine, Division of Immunology and Allergic Diseases, Istanbul University Faculty of Medicine, Istanbul, Turkey

Corresponding Author: Nida Öztop ✉ nida_oztop@hotmail.com

ABSTRACT

Objective: To evaluate the clinical outcome of omalizumab in various diseases.

Materials and Methods: Patients receiving at least one dose of omalizumab for chronic spontaneous urticaria (CSU), severe allergic asthma (SAA), nasal polyposis (NP) with asthma, idiopathic anaphylaxis (IA), mastocytosis, or allergic bronchopulmonary aspergillosis (ABPA) were retrospectively included. The effectiveness of omalizumab was assessed with asthma control test (ACT) at baseline and 16th week of treatment in SAA and ABPA. Urticaria activity score-7 (UAS7) and medication scores (MS) in CSU and SCORMA (SCORing MAstocytosis) index in mastocytosis were determined at baseline, the 3rd and 6th months of treatment. Nasal endoscopy for NP was performed at baseline and at the 6th month and first year of treatment. Clinical assessments at baseline and during treatment were performed for IA.

Results: A total of 213 patients were included. In 59 patients with SAA (27.6%), ACT scores significantly increased at the 16th week ($p<0.001$). Omalizumab was discontinued at a median duration of 15 months (min-max: 6-111) in 10 (16.9%) patients whose asthma was under control. In 4 of them, omalizumab had to be restarted at a median of 6 (min-max:3-12) months. In 141 patients with CSU, the baseline UAS7 and MS were significantly higher than those at the 3rd and 6th months ($p<0.001$). The treatment interval was increased to 45 days at the 6th month in 77 (55.8%) patients and 40 of them presented with relapse in a mean duration of 37.98±2.3 days. Five patients with ABPA, 4 patients with IA and 2 patients with NP and asthma were under control at their assessment visits. In 2 patients with mastocytosis, the SCORMA index was significantly lower at the 6th month ($p=0.04$). Thrombocytopenia and anaphylaxis were the confirmed adverse reactions seen during treatment.

Conclusion: This study demonstrates the effectiveness and safety of omalizumab in various diseases in long-term use in a real-life practice.

Keywords: Anaphylaxis, ABPA, severe asthma, chronic spontaneous urticaria, mastocytosis, nasal polyposis, omalizumab

INTRODUCTION

Omalizumab, a recombinant humanized monoclonal antibody which binds human immunoglobulin E (IgE) selectively (1) and inhibits the activation of highly selective IgE receptors on mast cells, has been used in several allergic and non-allergic diseases for almost twenty years (2). Up to now, many clinical trials have shown its effectiveness and safety in severe allergic asthma and have placed severe allergic asthma as its main indication worldwide (3-6). However, we still face open-ended questions regarding the continuation or cessation of omalizumab treatment in long-term use.

Another well-established indication of omalizumab is chronic spontaneous urticaria (CSU), which is resistant to high dose antihistamines (7). According to the recent EAACI/GA^{2}LEN/EDF/WAO urticaria guideline and the Turkish National Urticaria Guideline, 300 mg omalizumab every 4 weeks is the recommended treatment in patients who are unresponsive to 4 times the standard dose of antihistamines (7,8). In contrast to asthma, the effective

ORCID Nida Öztop / 0000-0003-2607-3833, Semra Demir / 0000-0003-3449-5868, Şengül Beyaz / 0000-0002-1505-4293, Özdemir Can Tüzer / 0000-0002-8028-2647, Bahauddin Çolakoğlu / 0000-0002-1851-9826, Suna Büyüköztürk / 0000-0002-1899-5566, Aslı Gelincik / 0000-0002-3524-9952

dose of omalizumab treatment in CSU is determined independent of the patient's body weight and the serum total IgE level (7). Similar to asthma, there is no consensus regarding the duration of omalizumab treatment in CSU (9).

Off-label use of omalizumab is also considered in various diseases (10). Omalizumab has been shown to be effective and safe in patients with allergic bronchopulmonary aspergillosis (ABPA), an allergic pulmonary disease caused by *Aspergillus fumigatus* (10), requiring long-term corticosteroid (CS) use (11). Omalizumab can also be effective in patients with recurrent nasal polyposis (NP) as a refractory component of chronic rhinosinusitis (CRS) who need recurrent or long-term use of CSs or frequent nasal surgeries (12). Idiopathic anaphylaxis, a life- threatening hypersensitivity reaction appearing without any identified triggers, is another important off-label use of omalizumab (10,13,14). Treatment of idiopathic anaphylaxis includes long-term use of antihistamines, systemic CSs or mast cell (MC) stabilizers to prevent recurrence of attacks and epinephrine to treat acute attacks (14,15). Furthermore, omalizumab can be considered as a promising option in such patients in order to prevent the adverse effects of CSs (16). Omalizumab can also be used off-label in mastocytosis for MC-related symptoms including skin lesions, anaphylaxis, gastrointestinal symptoms that are persistent despite of high dose antihistamines, steroids and MC stabilizers (17).

Clinical experience with omalizumab, the first approved biological agent for allergic and allergy-related conditions, in various populations is valuable to increase the knowledge on its dosage, duration of treatment, and adverse effects in various diseases in clinical practice. Therefore, we aimed to evaluate the clinical outcome of all the patients undergoing omalizumab treatment, including its safety profile and effectiveness in various indications at our tertiary clinic.

MATERIALS and METHODS

Patient Recruitment and Study Design

Patients older than 18 years of age who had received at least one dose of omalizumab for any of the conditions of CSU, severe allergic asthma, NP, idiopathic anaphylaxis, mastocytosis, or ABPA between August 2010 and December 2020 at the adult allergy outpatient clinic of the Istanbul Faculty of Medicine were included retrospectively to the study.

The demographic, clinical and laboratory features including clinical scores evaluating clinical severity measured prior to omalizumab and at the 16th week or 3rd and 6th months of treatment were collected from medical records. Doses and duration of omalizumab, any adverse events developed during treatment, recurrence of urticaria or worsening of asthma symptoms and the time period between recurrence of symptoms and treatment cessation in those whose treatment was stopped, were recorded. All SAA patients who received omalizumab treatment had an atopy, and atopy was defined according to the presence of one positive skin prick test result to aeroallergens including pollens, dust mite, *Aspergillus fumigatus* or *Alterneria alternata* (Allergopharma, Germany) or having a high serum specific IgE level to any of them (ImmunoCap, Phadiatop, Sweden).

Patients who had been prescribed omalizumab for their severe allergic asthma presenting with exacerbations within the last year or poor symptom control despite having received high dose inhaled corticosteroids (ICS) combined with long-acting beta-agonist agents (LABAs) or maintenance of oral corticosteroids (6,18) were evaluated with the Asthma Control Test (ACT) and were grouped into three groups as having fully controlled, partially controlled, or uncontrolled asthma (19). In patients with confirmed ABPA as determined by high serum total IgE levels, findings in chest computed tomography, positive skin prick test results to *Aspergillus fumigatus* or high serum specific IgE levels of *Aspergillus fumigatus*, the asthma control level was also determined with ACT (20). The dosage of omalizumab was determined according to the patient's serum total IgE level and weight in both patients with asthma and ABPA (18). Baseline ACT results and those at the 16th week of omalizumab treatment were evaluated.

CSU patients receiving omalizumab treatment were grouped into four groups as having controlled, mild, moderate, or uncontrolled CSU according to their Urticaria Activity Score-7 (UAS-7) scores. Accordingly, UAS-7 scores below or equal to 6 and scores between 28 and 42 were considered to determine well-controlled and uncontrolled CSU, respectively. UAS-7 scores between 7-15 or 16-27 revealed mild or moderate CSU, respectively (21). CSU patients were evaluated by the UAS-7 scores three times during the study period: prior to treatment, and at the 3rd and 6th months of omalizumab. The initial dose of omalizumab was determined as 300 mg every

4 weeks in all CSU patients as suggested by the EAACI/GA²LEN/WAO and Turkish National urticaria guidelines (7,8). Concomitant medication need for CSU symptoms was determined with a medication score assessment three times: prior to omalizumab treatment and at the 3rd and 6th months of omalizumab. Accordingly, the following scores were applied for each drug: antihistamines (regular dose, 2 points; 4 times regular dose, 8 points), CSs (prednisone <11 mg or equivalent, 5 points; prednisone 11-25 mg or equivalent, 10 points; prednisone >25 mg or equivalent, 15 points), cyclosporine (3 mg/kg, 8 points), hydroxychloroquine (6 points), and montelukast (2 points) (22).

In patients with NP and CRS, the presence of symptoms including loss of the sense of smell, nasal congestion, or rhinorrhoea was queried and endoscopic evaluation of the nasal cavity was performed by an ENT specialist before omalizumab treatment and after six months after treatment.

Patients having idiopathic anaphylaxis episodes diagnosed according to the World Allergy Organization (WAO) criteria (23) after exclusion of mastocytosis despite receiving high dose antihistamines and MC stabilizers were included in the study and were prescribed 300 mg of omalizumab per month. Efficacy of omalizumab treatment was determined according to the number of anaphylaxis episodes during treatment.

In patients with mastocytosis whose skin lesions were persistent despite a high dose of antihistamines, topical steroids, and MC stabilizers, diagnosed according to the WHO 2016 diagnostic criteria (24), 300 mg omalizumab per month was prescribed. Efficacy of omalizumab for skin lesions in mastocytosis was determined according to the SCORMA (SCORing MAstocytosis) index (25), prior to omalizumab treatment, and at the 3rd and 6th months of omalizumab treatment.

This study was approved by the Istanbul University Faculty of Medicine ethics committee (Approval number: 62255). For presenting the data of off-label use in the manuscript, approval from the Ministry of Health, Pharmaceutical and Medical Devices Institution was also obtained (Approval number: 66175679-514.99-E.229968).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Inc. Armonk, NY, USA) v22.0, and the GraphPad Prism Software 8 (San Diego, CA, USA) was used for graphics. Demographic and clinical features were assessed by descriptive analysis and shown as percentages and mean± standard deviation or median according to the distribution of the data. Continuous variables were compared by the independent t test or Mann-Whitney U test between two groups, depending on the distribution of the data. The categorical variables were compared with the X^2 test. A p value less than <0.05 was considered significant.

RESULTS

After excluding the patients with missing data, a total of 213 patients (141 CSU patients, 59 asthmatic patients, 5 patients with ABPA, 4 patients with idiopathic anaphylaxis, 2 patients with NP, and 2 patients with mastocytosis) were included in the study. The demographic and clinical characteristics of the patients distributed according to different omalizumab indications are summarized in Table I. A total of 159 (74.5%) patients were female and the mean age was 42.13±12.33 years; 56 (27.4%) patients had a history of a concomitant disease as shown in Table I.

Clinical Findings in Severe Allergic Asthma Patients

1. Effectiveness of Omalizumab

Fifty nine patients with severe allergic asthma were treated with omalizumab and the median values of the serum total IgE level and blood eosinophil counts were 217 (37-4483) kU/L and 240 (0-1500) /ųL, respectively (Table I). Eighty seven point five percent (n=54) of the patients had positivity in their skin prick test for house dust mites, and atopy was confirmed with high serum specific IgE levels for house dust mites in 6 patients. All patients were on high dose ICS before omalizumab treatment and the most commonly used ICS was fluticasone (n=27). The mean dose of LABA was 751.86±248.66 mcg. Salmeterol (n=27) and formoterol (n=32) were the pre-treatment LABA preferences. Before the beginning of omalizumab treatment, ACT scores were £19 and 20-24 in 55 and 4 patients, respectively. At the 16th week of omalizumab treatment, ACT scores of 25, 20-24 and £19 were found in 44, 13, and 2 patients, respectively. The mean baseline ACT scores and the scores at the 16th week of omalizumab treatment were 6.76±3.49 and 19.27±5.56, respectively (p<0.001) (Figure 1).

2. Follow-Up of the Omalizumab Treatment

Omalizumab treatment was discontinued at a median time of 15 months (min-max: 6-111) in 10 (16.9%) patients

Table I: Patients' demographic and clinical characteristics according to the different indications of omalizumab.

Features	CSU (n=141)	Severe allergic asthma (n=59)	ABPA (n=5)	Idiopathic anaphylaxis (n=4)	Nasal polyposis (n=2)	Mastocytosis (n=2)
Gender						
Female, n (%)	104 (73.8)	46 (77.6)	4 (80)	2 (50)	1 (50)	1 (50)
Male, n (%)	37 (26.2)	13 (22.4)	1 (20)	2 (50)	1 (50)	1 (50)
Age (mean±SD, year)	40.27±11.51	45.98±13.1	49.60±14.38	42.25±17.85	40.0±11.31	53.5±21.92
Body weight (mean±SD, kg)	70.81±12.06	73.05±14.00	73.8±14.46	70.5±14.48	73.5±16.26	76.5±4.95
Serum total IgE level [median (min-max), kU/L]	140 (3-4137)	217 (37-4483)	1216 (15-2426)	61 (50-84)	203.5 (187-220)	46.2 (14.4-78.0)
Blood eosinophil count [median (min-max), /ųL]	100 (10-900)	240 (0-1500)	220 (50-1200)	160 (110-200)	300 (100-500)	0 (0-0)
Duration of disease (mean±SD, month)	42.96±28.33	35.83±28.47	10.4±3.33	35.0±24.46	33.5±19.09	72.0±0.0
Duration of omalizumab treatment (mean±SD, month)	15.36±6.85	29.83±28.92	7.4±3.36	29.0±21,61	25.0±22.62	6.0±0.0
Omalizumab dosage (mean±SD, mg/month)	293.48±74.43	425.43±289.07	900.0±424.26	300.0±0.0	187.5±53.03	300.0±0.0
Presence of atopy, n (%)	28 (19.9)	59 (100)	5 (100)	1 (25)	2 (100)	0 (0)
Presence of comorbid diseases, n (%)	35 (24.8)	19 (32.2)	2 (40)	0 (0)	0 (0)	1 (50)

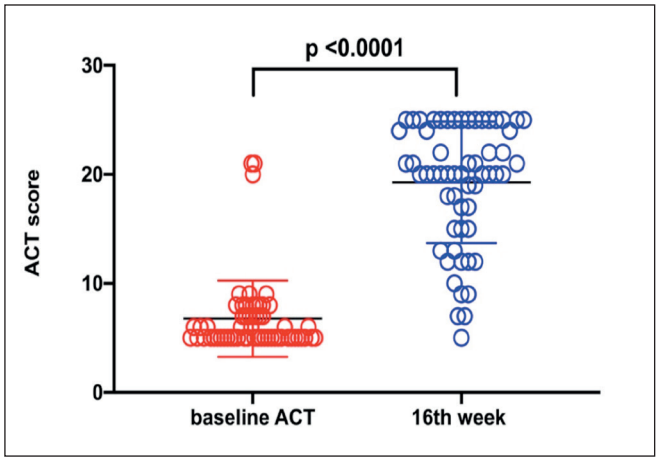

Figure 1. Comparison of the ACT scores at baseline and the 16th week of omalizumab in patients with severe allergic asthma.

whose asthma was under control. In 4 of them, omalizumab had to be restarted due to worsening of asthma symptoms at a median of 6 (min-max:3-12) months presenting as increased shortness of breath or admission to an emergency room. In patients with and without worsening of asthma after cessation of omalizumab, no significant difference was found regarding serum total IgE values, blood eosinophil counts, and demographic factors such as age and weight (p>0.05) (Table II).

Clinical Findings in CSU Patients

1. Effectiveness of Omalizumab

In 141 patients with CSU, the most commonly used high dose antihistamine was fexofenadine. None of the patients received cyclosporine or hydroxychloroquine treatment prior to omalizumab while 51.8% of the patients required short-term CS use during antihistamine treatment. The demographic, clinical and laboratory data of CSU patients are shown in detail in Table III.

The mean value of UAS-7 scores at baseline, the 3rd month and the 6th month of omalizumab treatment were 38.27±3.93, 3.47±4.83 and 1.96±4.55, respectively. The baseline UAS7 and medication scores were significantly higher than those at the 3rd and 6th months of the treatment (p<0.001) (Figure 2) .

Table II: Comparison of clinical and demographic data of asthma patients with worsening or remission after cessation of omalizumab.

Features	Patients with worsening of symptoms (n=4)	Patients in remission (n=6)	p
Gender Female, n (%) Male, n (%)	 3 (75) 1 (25)	 5 (83.3) 1 (16.7)	 NS
Age (mean±SD, year)	48.25±8.34	46.17±14.62	NS
Body weight (mean±SD, kg)	80.0±14.72	69.67±13.35	NS
Baseline serum total IgE level [median (min-max), kU/L]	92(46.6-402)	241.5 (60-957)	NS
Blood eosinophil counts [median (min-max), /μL]	210 (100-300)	100 (0-220)	NS
Duration of disease [median (min-max), year]	48.0±36.31	37.67±40.47	NS
History of allergen immunotherapy, n (%)	0 (0)	2 (100)	NS
Baseline ACT (mean±SD)	6.0±1.15	6.83±1.32	NS

ACT: Asthma Control Test, **NS:** Non-significant, **SD:** Standard Deviation.

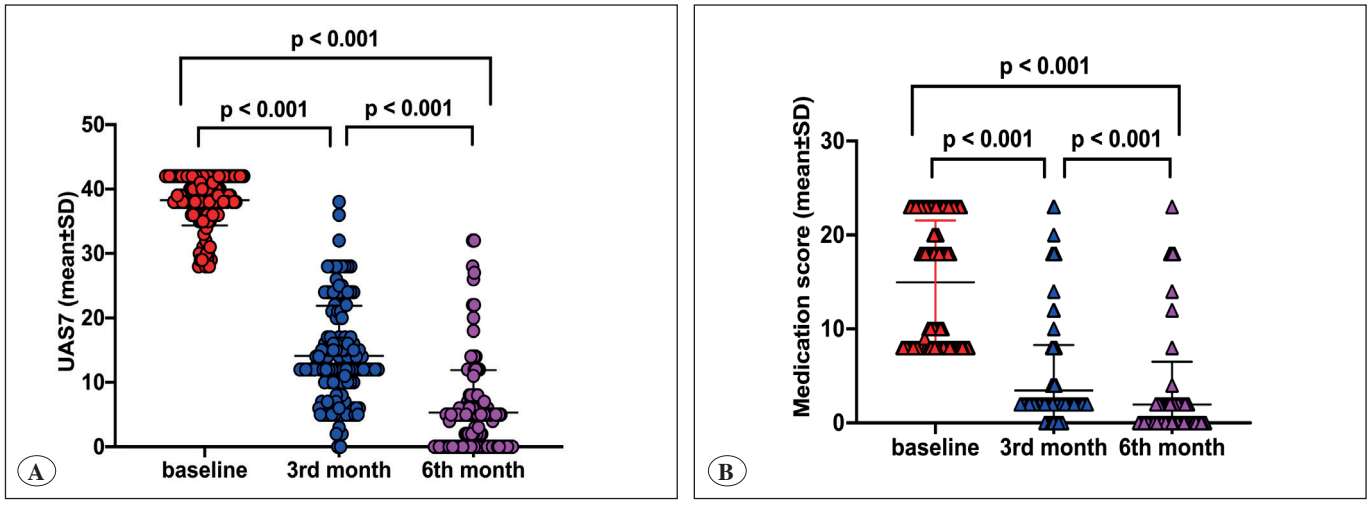

Figure 2. Comparison of the mean UAS7 **(A)** and medication scores **(B)** at pre-treatment, and the 3rd and 6th month of omalizumab treatment in CSU patients.

2. Follow-Up of the Omalizumab Treatment

All patients with CSU were started treatment with 300 mg of omalizumab per month. At the 3rd month control visit, the treatment was continued with 150 mg every 2 weeks in 17 patients whose symptoms recurred within 15 days after omalizumab injections and were thereafter controlled with this dose adjustment. The treatment interval was increased to 45 days at the 6th month in 77 (55.8%) patients whose symptoms were under control. Since 40 of them presented with relapse within 37.98±2.3 days, the interval between the injections was decreased to a month again. Omalizumab doses were increased to 450 mg/month and 600 mg/month depending on the body weight and baseline serum total IgE levels as suggested in asthma in the 3rd month of treatment in 6 and 2 patients, respectively because they were unresponsive to the initial dose of 300 mg/month omalizumab and concomitant high dose antihistamine treatment. In 4 of these patients whose pre-omalizumab skin biopsy revealed mixed neutrophilic and eosinophilic infiltrations and where urticaria recurred under high dose of omalizumab treatment, we changed our treatment strategy to administer cyclosporine. In one of these 4 CSU patients, the treatment was replaced by 100 mg of cyclosporine whereas 4-fold antihistamine was continued since exacerbation was seen one day after

the second dose of 300 mg omalizumab and in another patient whose urticaria episodes were not under control after 3 months of 450 mg omalizumab. After 6 months of omalizumab treatment, cyclosporine 100 mg was added to the treatment in the remaining 2 patients who were under omalizumab 450 mg/month and 600 mg/month respectively and partially responsive to omalizumab. The urticarial attacks were under control in these patients with this strategy. Different dose adjustment regimens of omalizumab used in patients with CSU are shown in Figure 3.

Omalizumab treatment was discontinued in 59 patients in remission at a mean of 12.97±6.99 months. After cessation of omalizumab, urticaria recurred in 10 patients at a mean of 5.50±2.75 months. In comparison of the demographic and clinical features of the patients with or without recurrence, we observed that the duration of the disease was significantly longer in patients with recurrence than in patients in remission (p<0.001) (Table IV).

In one CSU patient, pregnancy was noticed at the 3rd dose of omalizumab 300 mg and treatment was discontinued because of the patient's request. After cessation of omalizumab since urticaria attacks appeared under 4-fold dose of antihistamine, the same dose of omalizumab was restarted. She successfully gave birth vaginally and no complication developed during pregnancy or birth. No complication was also seen in the fetus.

Effectiveness and Follow-Up of Omalizumab Treatment in Patients with Off-Label Use

Five patients with ABPA were treated with omalizumab. None of them had a history of an underlying lung disease. The mean age was 49.60±14.38 years (Table I). The median serum total IgE level and specific IgE to *Aspergillus fumigatus* were 1216 (15-2426) kU/L and 2 (1,5-44.8) kU/L, respectively. All patients received itraconazole 400 mg/daily and oral methylprednisolone 32 mg/day before omalizumab treatment. All the patients were under high dose ICS and LABA combination (fluticasone+salmeterol in 3 patients, budesonide +formoterol in 2 patients) treatment. ACT scores were less than 19 at the beginning of the treatment in all patients. Since the doses of omalizumab were adjusted according to the weight and total IgE levels as suggested in asthma, one patient received 300 mg/month, another received 600 mg/month and three patients received 600 mg /every 15 days. At the 16th week of omalizumab therapy, ACT scores increased to 25 and

Table III: Demographics and clinical characteristic of CSU patients treated with omalizumab

Features	Values
Age (years, mean±SD)	40.27±11.51
Body weight (kg, mean±SD)	70.7±12.02
History of	
Atopy, n (%)	26 (18.7)
NSAID hypersensitivity, n (%)	20 (14.4)
Food hypersensitivity, n (%)	11 (7.9)
Concomitant angioedema, n (%)	52 (37.4)
Concomitant dermographism, n (%)	8 (5.8)
Antithyroid peroxidase [median (min-max), IU/mL]	12.5 (0-787)
Missing, n (%)	17 (23.7)
Antithyroglobulin [median (min-max), IU/mL]	12 (10-864)
Missing, n (%)	17 (23.7)
Antinuclear antibody titer	
Positive, n (%)	9 (6.4)
Negative, n (%)	129 (91.5)
Missing, n (%)	3 (2.1)
Treatments before omalizumab	
H1 antihistamines, n (%)	141 (100)
H1 antihistamines+glucocorticoids, n (%)	71 (51.1)
H1 antihistamines+montelukast, n (%)	25 (18.4)
UAS-7	
Prior to treatment with omalizumab (mean±SD)	38.27±3.93
3rd month of omalizumab (mean±SD)	14.14±7.77
6th month of omalizumab (mean±SD)	5.35±6.59
Medical assessment score	
Prior to treatment with omalizumab (mean±SD)	14.96±6.59
3rd month of omalizumab (mean±SD)	3.47±4.83
6th month of omalizumab (mean±SD)	1.96±4.55

NSAID: Non-steroidal anti-inflammatory drug, **UAS-7:** Urticaria Activity score for 7 days, **SD:** Standart Deviation.

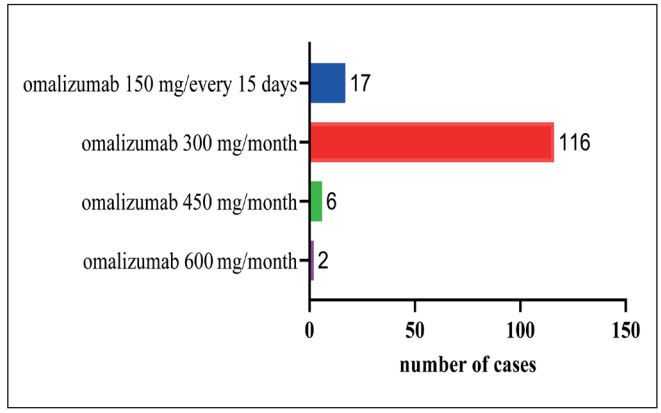

Figure 3. Number of patients who were treated with different doses of omalizumab in CSU after the 3rd month.

Table IV: The comparison of the demographic and the clinical characteristics of CSU patients with and without recurrence after omalizumab cessation.

Features	The patients with recurrence (n=10)	The patients without recurrence (n=49)	p
Gender Female, n (%) Male, n (%)	 9 (18.8) 1 (9.1)	 39 (81.2) 10 (90.9)	 NS
Age (mean±SD, year)	37.10±11.2	41.65±13.21	NS
Body weight (mean±SD, kg)	71.70±13.09	69.69±12.38	NS
Baseline serum total IgE level [median (min-max), kU/L]	80 (3-514)	171 (8.5-4137)	NS
Baseline antithyroid peroxidase [median (min-max), IU/mL]	17.25 (0.50-452)	13 (6-226)	NS
Baseline antinuclear antibody titer Positive, n (%) Negative, n (%) Missing, n (%)	 0 (0) 10 (100) 0 (0)	 5 (10.2) 42 (85.7) 2 (4.1)	 NS
Blood eosinophil counts [median (min-max), /μL])	97.0±90.06	141.06±167.82	NS
Duration of disease (mean±SD, months)	60.7±28.79	32.47±21.05	**0,001**
Concomitant angioedema, n (%)	6 (33.3)	12 (66.7)	NS
NSAID hypersensitivity, n (%)	1 (10)	9 (90)	NS
Food hypersensitivity, n (%)	2 (40)	3 (60)	NS
UAS7 scores prior to omalizumab treatment	39.90±2.07	38.33±4.00	NS

20-24 in 3 and 2 patients, respectively. In all patients, systemic CSs and itraconazole could be discontinued at the 3rd month of omalizumab treatment.

Omalizumab was prescribed to 4 patients with idiopathic anaphylaxis who required long-term systemic CSs and 4-fold antihistamines to control their attacks. Their mean age was 42.25±17.85 years (Table I). The median serum total IgE level and baseline tryptase levels were 61.35 (50-84) kU/L and 4.77 (3.5-7.5) μg/L, respectively. In all patients, systemic mastocytosis was excluded with a normal tryptase level and the absence of the c-kit mutation. None of them had any concomitant disease. All patients with idiopathic anaphylaxis were treated with omalizumab 300 mg monthly, independent of their initial total IgE level and body weight. None of them had an anaphylaxis attack at the 3rd month of omalizumab treatment. Antihistamines and glucocorticoids were discontinued in all patients at 3 months. During follow-up, omalizumab was not discontinued in any patient and none of them had anaphylaxis episodes.

Two patients with NP and asthma were treated with omalizumab due to the frequent recurrence of NP. Their mean age was 45.98±13.1 years (Table I). Both patients had grade 4 polyposis and had undergone surgical polypectomy more than twice despite receiving nasal steroids and montelukast. They had no hypersensitivity to any non-steroidal anti-inflammatory drugs. Both patients had positive skin prick test results for aeroallergens. The median serum total IgE level was 203 (187-220) kU/L. Omalizumab, determined depending on the initial weight and serum total IgE level as suggested in asthma, was added onto their therapy after nasal polypectomy. Both of them were treated with 300 mg/ month of omalizumab. At the 6th month and the first year of omalizumab treatment, no new polyposis was detected in either patient.

Two patients with mastocytosis were treated with omalizumab 300 mg /monthly during the study period due to persistent skin lesions despite having received high dose antihistamines, topical and systemic CSs, and MC stabilizers for 6 months. Their mean age was 53.5±21.92 years (Table I) and the mean baseline serum tryptase level was 43.75±23.26 μg/L. One patient had cutaneous mastocytosis and the other patient had indolent systemic mastocytosis. The mean value of SCORMA indexes at baseline, and the 3rd and the 6th months after omalizumab

treatment were 63.8±0.28, 39.8±15.55 and 20.7±17.39, respectively. The SCORMA index was significantly lower at the 6th month of omalizumab than the baseline levels (p=0.04). There were no statistically significant difference between serum tryptase and total IgE levels at baseline, and the 3rd and 6th months of omalizumab treatment (p>0.05).

Safety of Omalizumab in the Study Population

A total of 5 adverse events were observed during omalizumab treatment. In a 69-year-old female patient with severe allergic asthma, thrombocytopenia developed at the 6th month of treatment. The platelet counts were normal before omalizumab treatment. After 6 months of omalizumab, thrombocytopenia was detected in the routine visit. There was no petechiae or hemorrhage. All viral serology was negative. It was considered a drug-related immune thrombocytopenia by a haematologist, and stopping omalizumab treatment was suggested. Her platelet count increased to a normal level with systemic CSs after cessation of omalizumab.

Among CSU patients at the 3rd month of treatment, endometrial *in situ* carcinoma was detected at routine screening in a 38-year-old patient and stage-1 pancreatic cancer was diagnosed while investigating the reasons of marked weight loss in one month in a 55-year-old female patient. Omalizumab was stopped in these patients and they were treated with daily high dose antihistamines and on demand CSs. For both of these patients, it is difficult to establish a cause and effect relationship between their cancer and omalizumab since both genetic and environmental risk factors can play a role in the development of these cancers.

In a 26-year-old female patient with CSU, exacerbation of urticaria plaques was seen one day after the second dose of 300 mg omalizumab. After an attack treatment with CSs, omalizumab was changed to cyclosporine. However, the response to treatment could not be assessed since she did not come to the follow-up visits afterwards. This patient can also be considered as an unresponsive CSU patient to omalizumab but it is difficult to make a conclusive remark since the patient did not come to her follow-up visits.

In a 24-year-old female patient with CSU, anaphylaxis occurred after the 18th omalizumab dose at the 5th hour of injection. She was observed 2 hours after omalizumab injection in our clinic for possible adverse effects and there were no symptoms. After leaving the hospital, at the 5th hour of injection, she had shortness of breath, dizziness, flushing and syncope. She presented to an emergency unit where intramuscular adrenaline was administered but the serum tryptase level could not be measured at this attack. The patient could not recognise any triggers for anaphylaxis. Due to this definite history, omalizumab was considered as the cause of anaphylaxis and the treatment was stopped. She was continued to be treated with daily high dose antihistamines and on demand CSs.

DISCUSSION

The current study presents the effectiveness and safety of omalizumab in clinical practice in various diseases considered either as well-described indications or off-label use of omalizumab. It also demonstrates the usefulness of individual dose adjustments in CSU whereas the efficiency of the initial dose arrangement depending on the body weight and baseline serum TIgE level during the course of severe allergic asthma was observed in a real-life practice. Furthermore, the duration of CSU seems to be playing a role on the exacerbation frequency seen after withdrawal of omalizumab treatment whereas no significant demographic and clinical findings play a role on the worsening of severe allergic asthma after cessation of omalizumab.

Current knowledge on omalizumab treatment in nearly all real-life studies reveals the effectiveness and safety of omalizumab in severe allergic asthma (6,26,27). In a recent real-life study, 1687 severe allergic asthmatic patients were treated with omalizumab for a year and omalizumab was effective and safe for the study period (28). Another study included 465 patients who were treated with omalizumab due to severe allergic asthma for five years and found promising results on effectiveness and safety (27). In all these studies, no criteria for making the decision of continuation or cessation of omalizumab have been addressed. In our study, omalizumab treatment was effective for controlling asthma in the majority of patients evaluated at the 16th week of treatment. In four out of ten patients whose omalizumab treatment was discontinued due to control of asthma achieved at a median of 15 (min-max:6-111) months, worsening of asthma led them to be hospitalized and omalizumab was restarted. The time interval between the deterioration of symptoms and the cessation of omalizumab was 6 months in two patients and 3 months and 1 year in two other patients, respectively. When comparing the possible reasons of deterioration

among the demographic and clinical features between patients with and without worsening of asthma, no significant relation was observed. Since we do not have any data on the optimal duration of omalizumab in severe allergic asthma, our findings outlined the importance of an individual approach for every single patient for deciding the duration of omalizumab treatment in severe allergic asthma.

Similar to recent studies (22,29), the UAS-7 scores and the need for concomitant medications used daily were significantly decreased in the 3rd and 6th months of omalizumab treatment together with the related side effects of medications in our study. The updosing of omalizumab was found to be related to higher initial UAS7 scores and higher baseline BMI in another study (29). Another study has revealed that omalizumab was effective in the majority of the patients even after the first week of injection in 14 CSU patients treated with omalizumab with doses arranged according to the baseline serum total IgE level and body weight (30). In 8 of our CSU patients with uncontrolled symptoms with omalizumab 300 mg per month, the dose was increased to 450 mg/month (n=6) and 600 mg/month (n=2) depending on the patients' serum total IgE level and body weight. Since half of these patients failed to respond to the 3rd doses of omalizumab, cyclosporine was initiated either as a concomitant therapeutic option or alone and found to be successful after confirmation of neutrophilic infiltration in skin biopsy samples. Cyclosporine can be used in CSU as a third line therapy but it is not licensed and has some adverse effects (31). Eventually, doses adjusted according to the initial serum total IgE levels and body weight can be beneficial when CSU cannot be controlled with the standard initial dose of omalizumab, according to our findings. Otherwise, cyclosporine can be included in the treatment after confirmation of neutrophilic inflammation in skin lesions. We believe taking a biopsy before the initiation of cyclosporine is important, considering the side effects of cyclosporine and the duration of the treatment. In conclusion, our findings suggest that dose adjustments in omalizumab treatment during CSU follow-ups may be necessary to achieve disease control unlike severe asthma treatment.

There is no consensus for duration of omalizumab treatment in CSU and the risk factors for the recurrence of urticaria after cessation are not known. In a recent study, it was shown that complete remission with omalizumab could be achieved in CSU in 12 weeks, while patients who did not experience complete remission could achieve full remission within 13-24 weeks (32). In our study, omalizumab treatment could be discontinued in 12.97±6.99 months in 59 patients with CSU whose diseases were under control and urticaria recurred in 10 patients in 5.50±2.75 months after cessation of omalizumab. While CSU duration longer than three years was found to be related to recurrence, NSAID hypersensitivity and the presence of angioedema or atopy did not seem to be important. In contrast to another study in the literature, in which serum basal total IgE levels before omalizumab treatment in CSU were reported to be negatively correlated with the duration of relapse after discontinuation of omalizumab (33), there were no significant differences between the serum baseline total IgE levels in CSU patients with or without recurrence after cessation of omalizumab in the current study. Maurer et al. have reported that having higher serum IgE levels, a higher ANA positivity rate, and higher baseline anti-TPO levels with longer disease duration time could be seen in type IIb autoimmune CSU patients, and that type II autoimmune CSU patients may have slow response to omalizumab treatment (34). In our study, the baseline serum total IgE levels, baseline anti-TPO levels, baseline ANA positivity ratio, and baseline UAS7 scores were not different between those with and without recurrence in the CSU groups. In accordance with this finding, we could not differentiate between type 1/type IIb autoimmune CSU in our patients. However, our statistics may not have been significant since there was no numerical equality between the patients with and without recurrence. CSU patients with recurrence had a longer disease duration than those without recurrence in the recurrence study. Although the evidence level is low (34), a longer disease duration time may lead to omalizumab treatment resistance. In accordance with these findings we may speculate that patients with longer disease duration should be observed closely for recurrence after cessation of omalizumab. Additionally, while stopping omalizumab treatment, it might be best to increase the injection intervals of omalizumab as much as possible and to observe if the patients can tolerate it. We believe that further studies with more patients are needed to explain the omalizumab treatment response in CSU patients with longer disease duration.

The knowledge on omalizumab in ABPA management is relatively sparse. Similar to our findings, some studies have shown its safety and effectiveness. As an example, omalizumab treatment improved asthma symptoms while decreasing serum total IgE levels and was very well

tolerated in ABPA in a study (11). Physicians mostly initiate omalizumab to prevent the side effects seen due to systemic steroids in ABPA patients who do not respond to the standard treatment (11). However, it is important to evaluate the presence of underlying diseases to achieve asthma control in ABPA. As an example, omalizumab treatment did not improve the outcomes of asthmatic symptoms in 9 patients with ABPA with underlying cystic fibrosis in a recent study (35). We suggest that omalizumab could be considered as a treatment option for those who need long-term systemic CSs in ABPA with well-established asthma.

Patients with idiopathic anaphylaxis whose attacks are resistant to antihistamines or MC stabilizers can successfully be treated with omalizumab with doses determined according to the patient's weight and serum baseline total IgE levels. However, similar to other diseases, the standard dose and duration of omalizumab treatment is not well-established yet (13,16,36). In our study, we have successfully treated 4 patients with idiopathic anaphylaxis whose attacks continued to occur under treatment with high dose antihistamines and long-term systemic CSs, with a standard dose of omalizumab 300 mg monthly similar to CSU patients. Although the number of patients in our study is too low to reach conclusions, this finding leads us to suggest using this strategy in idiopathic anaphylaxis. However, large cohort studies could clarify the optimal dose and duration of omalizumab in idiopathic anaphylaxis patients.

Omalizumab can be effectively used in the patients with frequent recurrent NP (37). In a study with 13 patients, it was shown that omalizumab treatment in chronic rhinosinusitis with NP and severe asthma could improve the symptoms of rhinosinusitis and asthma after polyp surgery and may prevent the recurrence of NP (38). In accordance with these studies, 2 patients with NP and severe asthma were treated with omalizumab due to resistance to standard treatment of NP after nasal surgery, and NP did not occur after omalizumab treatment in our study. Additionally, the asthma symptoms of these patients improved markedly. Regarding these findings, we believe that starting omalizumab treatment after medical or surgical polypectomy can be successful in preventing polyp recurrence.

Omalizumab can also be effective in mastocytosis. In a recent review including 69 mastocytosis patients, it was reported that a mean duration of 17 months of omalizumab treatment can be effective for cardiovascular, cutaneous and gastrointestinal symptoms but the effects on neuropsychiatric and musculosceletal symptoms can be limited (17). In another study, omalizumab's effectiveness was observed on MC-related symptoms and the mean duration of the best response was 6 months in 55 patients with mastocytosis (39). In our study, the SCORMA index was significantly lower in 2 patients with mastocytosis who were treated with omalizumab for 6 months due resistance of skin lesions to standard treatment, in accordance with the literature.

A few adverse events were observed during omalizumab treatment in our study. In a patient with severe allergic asthma, thrombocytopenia developed at the 6th month of treatment and was considered as a drug-related immune thrombocytopenia. In preclinical studies, omalizumab caused thrombocytopenia 3,5 to 20 more times in monkeys than in humans. However, no difference was found between patients treated with omalizumab and the control group in terms of development of thrombocytopenia in clinical studies (40). On the other hand, immune thrombocytopenia has been reported in a 13 year-old patient treated with omalizumab due to severe asthma, similar to our patient (41). In the EXCELL study, it was shown that omalizumab is not associated with an increased risk of malignancy (42). In our study, endometrial in situ carcinoma and stage-1 pancreatic cancer were detected at the 3rd month of treatment in 2 patients with CSU. Since these malignancies were detected in an early period of omalizumab treatment and several other factors could be responsible for this situation, a conclusive remark cannot be made. In our study, anaphylaxis was observed after the 18th omalizumab injection after 5 hours. Anaphylaxis due to omalizumab is extremely rare (43) but it is important for clinicians to be aware of such a situation.

As a limitation, the retrospective design of the study may cause a bias in data recall. The medical notes could also be missing in patient charts in the emergency room or in our outpatient clinic. We believe we have overcome this possibility by excluding patients with missing data. The effectiveness of omalizumab in asthma was not evaluated after the 16th week control. We believe more comprehensive prospective cohort studies may give more reliable results. However, the strength of our study is the evaluation of the clinical results of omalizumab in various diseases reflecting clinical practice in real life.

In conclusion, this study demonstrates the effectiveness and safety of omalizumab in various diseases and presents the clinical information regarding long-term use of omalizumab in a real-life practice. Large registries on the clinical practice of omalizumab in different diseases including different age groups will improve our knowledge on omalizumab and guide our clinical practice in future.

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This study was approved by Istanbul University Faculty of Medicine ethics committee (Approval number: 62255). For presenting the data of off-label use in the manuscript, approval from Ministry of Health, Pharmaceutical and Medical Devices Institution was also obtained (Approval number: 66175679-514.99-E.229968).

Authorship Contributions

Concept: **Nida Öztop, Semra Demir, Şengül Beyaz, Aslı Gelincik,** Design: **Nida Öztop, Semra Demir, Şengül Beyaz, Aslı Gelincik,** Data collection or processing: **Nida Öztop, Semra Demir, Şengül Beyaz, Özdemir Can Tüzer, Aslı Gelincik,** Analysis or Interpretation: **Nida Öztop, Semra Demir, Şengül Beyaz, Aslı Gelincik,** Literature search: **Nida Öztop, Şengül Beyaz,** Writing: **Nida Öztop, Semra Demir, Bahauddin Çolakoğlu, Suna Büyüköztürk, Aslı Gelincik,** Approval: **Nida Öztop.**

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