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The efficacy and safety of omalizumab in refractory chronic spontaneous urticaria: real-life experience in Turkey

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Abstract

Introduction: This study used real-world data to evaluate the effectiveness and reliability of omalizumab in treating recalcitrant chronic spontaneous urticaria in Turkish patients.
Methods: Study data were collected retrospectively from eight tertiary-care hospitals in Turkey. This study included 132 patients with chronic spontaneous urticaria that were resistant to H1 antihistamine treatment in a dose up to four times the licensed dose and were treated with 300 mg/month of omalizumab for 6 months.
Results: The mean weekly urticarial activity score (UAS7) after omalizumab treatment improved significantly compared to the pre-treatment score ($p < 0.001$). Treatment response was detected primarily in the 1st and 2nd months after treatment. No significant association was observed between omalizumab's treatment effectiveness and disease-related parameters or laboratory data. The mean dermatology life quality index was 23.12 ± 6.15 before treatment and decreased to 3.55 ± 3.60 6 months after treatment ($p < 0.001$). No side effects were reported in 89.4% (118) of the patients.
Conclusion: This study showed that UAS7 decreased significantly and quality of life improved in omalizumab-treated patients. Moreover, treatment effectiveness was mainly observed in the first 2 months after treatment. However, no association was observed between omalizumab treatment effectiveness and disease-related parameters or laboratory data.

Keywords: chronic spontaneous urticaria, omalizumab, dermatology life quality, UAS7, side effects

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Introduction

Chronic urticaria is urticaria that persists for longer than 6 weeks. Chronic spontaneous urticaria (CSU) is diagnosed by excluding inducible chronic urticaria as a possible diagnosis using the EAACI/GA²LEN/EDF/WAO guidelines (1). Approximately two-thirds of patients with chronic urticaria are CSU patients, and the incidence rate of CSU is between 0.5% and 1% worldwide (1). CSU reduces the quality of life of patients and is therefore an important health problem (2).

The first-line treatment of patients with CSU involves the use of non-sedative H_1 antihistamines. The licensed dose of these drugs can be increased up to fourfold in non-responding patients. Systemic steroids can be used at any time in patients showing an exacerbation of urticaria. However, one-third of patients do not respond to H_1 antihistamine treatment even when the standard dose is increased (3). Omalizumab, cyclosporine, and montelukast are suggested as a third-line treatment of patients with CSU that are resistant to the H_1 antihistamine treatment (1).

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to circulating free IgE heavy chains and indirectly downregulates FcεRI receptor expression on mast cells and basophils (4, 5). Clinical studies have shown the effectiveness of 150 and 300 mg/month omalizumab in patients with CSU (6). However, limited real-world data are available on the efficacy and safety of omalizumab. Therefore, this study evaluated the effectiveness and safety of omalizumab in Turkish patients with CSU that were resistant to second-line treatments.

Methods

This multicenter, retrospective study was carried out at eight tertiary care hospitals in Turkey and was approved by a local ethics committee. The study included patients that were diagnosed with CSU based on EAACI/GA²LEN/EDF/WAO guidelines, had a minimum disease duration of 6 months, did not respond to H_1 antihistamine treatment in a dose up to four times the licensed dose, and used 300 mg/month omalizumab for 6 months. Demographic data, disease-related parameters, and antibody levels were recorded retrospectively from patient records. The disease-related parameters included: disease duration, concomitant angioedema, concomitant dermographism, concomitant non-steroidal anti-inflammatory drug (NSAID) hypersensitivity, concomitant atopy (rhinitis, asthma, and dermatitis), autologous serum skin test (ASST) positivity, weekly urticarial activity score (UAS7), dermatology life quality index (DLQI), treatments administered before the omalizumab treatment, treatments administered concurrently with the omalizumab treatment, and side effects observed during the omalizumab treatment. Antibody levels were recorded for serum total IgE antibody, antinuclear antibody (ANA), antithyroglobulin (AntiT) antibody, and antithyroid peroxidase (AntiTPO). The threshold value for ANA positivity was set at ANA titers > 1:160.

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Patients that had been treated with a steroid for a minimum of 10 days and cyclosporin at a dose of 3 to 5 mg/kg/day for a minimum of 1 month were considered to have used those treatments.

Disease duration

Disease duration was divided into the following four categories for statistical evaluation: < 1 year; 1 year to < 5 years; 5 years to < 10 years; and ≥ 10 years.

UAS7 evaluation

The UAS7 was used to evaluate disease activity. Itching severity and urticarial plaque number were graded as follows: no itching = 0, mild itching = 1, moderate itching = 2, and intense itching = 3; no urticarial plaques = 0, 1–20 urticarial plaques = 2, 20–50 urticarial plaques = 3, and > 50 urticarial plaques = 4. The sum of 7 days of UAS values provided the UAS7 value. UAS7 scores were evaluated weekly, and an average of the scores from 4 weeks was used as the mean UAS7 for each month. Based on the UAS7 values, patients were classified as having severe CSU (UAS7: 28–42), moderate CSU (UAS7: 16–27), mild CSU (UAS7: 7–15), and well-controlled CSU (UAS7: 0–6) (1). Significant disease improvement was defined as a UAS7 value of < 6 after the omalizumab treatment (7). The UAS7 value before treatment and the mean UAS7 value each month after treatment were recorded to evaluate treatment response.

Quality of life assessment

DLQI scores were obtained at the beginning of the omalizumab treatment and 6 months after treatment to evaluate the quality of life of patients with CSU (8).

Omalizumab administration

Omalizumab injections were administered by experienced nurses at the tertiary-care hospitals. The patients were monitored for a potential anaphylactic reaction for two hours after administering each of the first three doses of omalizumab and for 30 minutes after administering subsequent doses.

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data are presented as percentages. The Shapiro–Wilk test was used to evaluate the normal distribution of data. The Mann–Whitney *U* test was used to compare two groups that did not show a normal distribution of data. Values obtained at different time points for the two groups were measured using the Wilcoxon test. Yate's chi-square correction was used to analyze cross tables. All statistical analyses were performed using the SPSS Statistics 21.0 program (IBM). A p value of < 0.05 was considered statistically significant.

Results

In all, 437 patients with CSU were evaluated. Of these, 305 were excluded because they did not meet the study eligibility criteria (Fig. 1). Thus, this study included 132 patients, of which 84 (63.6%) were women and 48 (36.4%) were men. The mean age was 39.2 ± 10.7 years (range 18–75 years). Disease duration was < 1 year in 42 (31.8%) patients, 1 to < 5 years in 74 (56.1%) patients, 5 to < 10 years in 11 (8.3%) patients, and ≥ 10 years in 5 (3.8%) patients. Urticaria was accompanied by angioedema in 31.8% of patients. Dermographism was observed in 33.3%, NSAID hypersensitivity was observed in 9.8%, and a history of atopy was observed in 16.7%. ASST positivity was observed in 65.9% of patients, and ANA positivity was observed in 4.5%. The mean serum IgE level was 54.4 ± 150.3 IU/ml (range 7.0–978.9 IU/ml). AntiT positivity was observed in 11.4%, and AntiTPO positivity was observed in 9.8% (Table 1).

The patients received the following treatments before receiving the omalizumab treatment: H_1 antihistamine treatment in up to four times the licensed dose (100% of patients), steroid treatment (62.1%), cyclosporine treatment (14.4%), montelukast treatment (0.8%), and other treatments such as narrow-band ultraviolet B, dapsone, azathioprine, and colchicine (5.4%; Table 1).

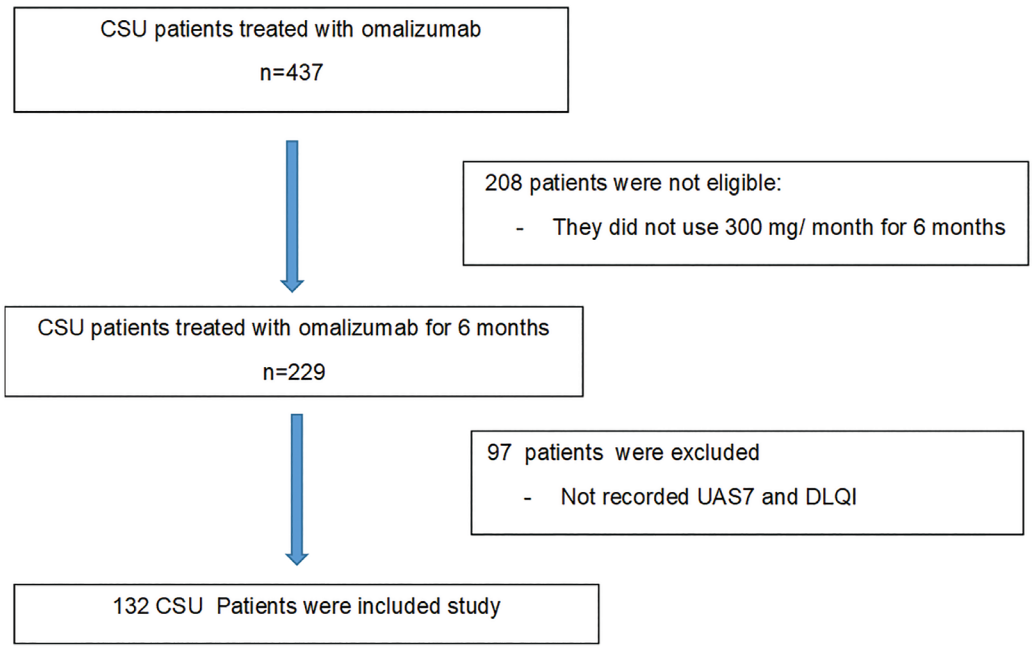

Figure 1 | Flowchart showing the eligibility criteria for patients included in the study.
CSU = chronic spontaneous urticaria, UAS7 = weekly urticarial activity score, DLQI = dermatologic life quality index.

Seventy-eight (59.1%) patients did not receive any other treatment with the omalizumab treatment. Omalizumab treatment was administered concurrently with the H_1 antihistamine treatment in 53 (40.1%) patients and with the cyclosporine treatment in one (0.8%) patient (Table 1).

Side effects

No treatment-related side effects were reported by 118 (89.4%) patients. However, one (0.8%) and 13 (9.8%) patients reported myalgia and nausea, respectively (Table 1).

Treatment response

The mean UAS7 value for the 132 patients was 30.5 ± 12.4 before omalizumab treatment and 1.5 ± 4.0 6 months after omalizumab treatment ($p < 0.001$; Table 1). Some patients responded to the treatment within only a few days. A significant difference was observed between the mean UAS7 value pre-treatment and the mean values 1 month and 2 months after treatment ($p < 0.001$; Table 2). However, no significant decrease in the mean UAS7 value was observed between the 2nd and 6th months after treatment (Table 2).

Of the 88 patients with severe disease based on the pre-treatment UAS7, 74 (84.1%) had well-controlled disease, 13 (14.8%) had mild disease, and a treatment response was not observed in one (1.1%) patient after 6 months of treatment (Fig. 2, Table 3). Of the 26 patients with moderate disease before treatment, 23 (88.5%) had well-controlled disease and two (7.7%) had mild disease after 6 months of treatment. All four patients with mild disease before treatment had their disease fully controlled after 6 months of treatment (Fig. 2, Table 3).

A comparison of the demographic data, disease-related parameters, and laboratory data of the patients that showed > 90% improvement 1, 3, or 6 months after treatment with those that did not indicated no statistically significant differences among these patients. The mean DLQI score was 23.1 ± 6.2 before treatment and 3.6 ± 3.6 after treatment, and the difference was statistically significant ($p < 0.001$).

Discussion

The treatment of chronic urticaria aims to control symptoms and improve quality of life. Although clinical studies have reported the efficacy and safety of omalizumab in patients with CSU, only a few studies involving a large number of patients and enough information have reported real-world data (9–13). In Turkey, omalizumab treatment for patients with CSU has been reimbursable since April 2014 and is used as the third-line treatment for CSU, following the EAACI/GA²LEN/EDF/WAO guidelines (1).

The study presented here evaluated UAS7 values and observed a marked response 1 month and 2 months after treatment with omalizumab. Although patient responses to treatment were classified according to months, some patients showed a response within a few days of treatment. This is consistent with the results of clinical studies and with real-world data reported in the literature (6, 14–22). Omalizumab decreases free IgE levels on mast cell surfaces and downregulates FcεR1 levels within 12 to 16 weeks (23, 24). Therefore, the early and rapid response of patients with CSU to omalizumab indicates the effectiveness of the treatment through various mechanisms. On the other hand, patients that show a poor response to omalizumab treatment should have their urticaria diagnosis re-evaluated.

Some studies have reported a complete response in 84.6% to

Table 1 | Demographic data and disease characteristics of the study patients.

Variable	Value
Sex	
Female	84 (63.6%)
Male	48 (36.4%)
Age (years)	
Median	39.0 (18–75)
Mean ± SD	39.2 ± 10.7
Disease duration (years)	
< 1	42 (31.8%)
1 to < 5	74 (56.1%)
5 to < 10	11 (8.3%)
≥ 10	5 (3.8%)
History of	
Angioedema	42 (31.8%)
Dermographism	44 (33.3%)
NSAID hypersensitivity	13 (9.8%)
Atopy	22 (16.7%)
ASST	
Negative	87 (28.8%)
Positive	38 (65.9%)
Not recorded	2 (1.5%)
ANA positivity	
Negative	110 (83.3%)
Positive	6 (4.5%)
Not recorded	16 (12.1%)
Serum IgE (IU/ml)	
Recorded	121.0 (91.7%)
Median	65.0 (7.0–978.0)
Mean ± SD	54.4 ± 150.3
Not recorded	11.0 (8.3%)
AntiT positivity	
Negative	112 (84.8%)
Positive	15 (11.4%)
Not recorded	5 (3.7%)
AntiTPO positivity	
Negative	114 (86.4%)
Positive	13 (9.8%)
Not recorded	5 (3.8%)
Treatments administered before omalizumab treatment	
H_1 antihistamines	132 (100.0%)
Systemic steroids	82 (62.1%)
Cyclosporine	19 (14.4%)
Montelukast	9 (6.8%)
H_2 antihistamine	1 (0.8%)
Other	
NB-UVB	3 (2.3%)
Azathioprine	2 (1.5%)
Dapsone	1 (0.8%)
Colchicine	1 (0.8%)
Treatments administered concurrently with omalizumab treatment	
None	78 (59.1%)
H_1 antihistamines	53 (40.1%)
Cyclosporine	1 (0.8%)
Side effect	
None	118 (89.4%)
Nausea	13 (9.8%)
Myalgia	1 (0.8%)
UAS7	
Pre-treatment	30.5 ± 12.4
Post-treatment	1.5 ± 4.0
DLQI	
Pre-treatment	23.1 ± 6.2
Post-treatment	3.6 ± 3.6

ANA = anti-nuclear antibody, AntiT = anti-thyroglobulin, AntiTPO = anti-thyroid peroxidase, ASST = autologous serum skin test, DLQI = dermatology life quality index, NB-UVB = narrow-band ultraviolet B, NSAID = non-steroidal anti-inflammatory drugs, UAS7 = weekly urticarial activity score.

Table 2 | **Comparison of pre- and post-treatment UAS7 values using the Wilcoxon signed rank test.**

UAS7 (n = 132)	Mean ± standard deviation Median (Q1–Q3)	p
Pre-treatment to month 1 post-treatment	30.54 ± 12.36 8.3 ± 10.92	< 0.001
Months 1 to 2 post-treatment	8.3 ± 10.92 4.86 ± 7.99	< 0.001
Months 2 to 3 post-treatment	4.86 ± 7.99 4.11 ± 7.48	0.900
Months 3 to 4 post-treatment	4.11 ± 7.48 3.34 ± 6.99	0.250
Months 4 to 5 post-treatment	3.34 ± 6.99 2.62 ± 6.25	0.141
Months 5 to 6 post-treatment	2.62 ± 6.25 1.52 ± 4.02	0.057

Table 3 | **Changes in treatment response according to disease severity using a marginal homogeneity test.**

Pre-treatment UAS7 values	UAS7 values at 6 months after treatment				p
	Well controlled	Mild disease	Moderate disease	Severe disease	
Well controlled	14 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	< 0.001
Mild disease	4 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Moderate disease	23 (88.5%)	2 (7.7%)	1 (3.8%)	0 (0.0%)	
Severe disease	74 (84.1%)	13 (14.8%)	0 (0.0%)	1 (1.1%)	

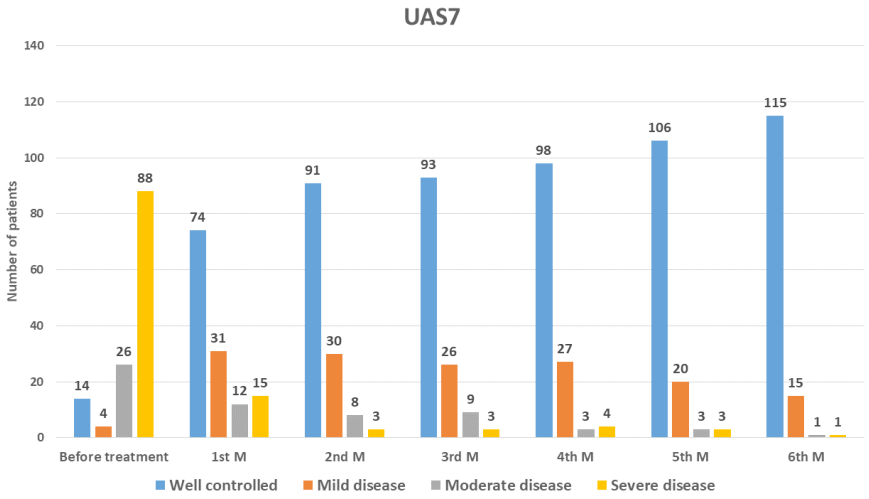

Figure 2 | Changes in the UAS7 score with treatment by month.
UAS7 = weekly urticarial activity score, M = month.

89.0% of patients (6, 12, 15, 16, 25). In this study, 87.1% of patients exhibited well-controlled disease and 78.8% of patients showed > 90% improvement in UAS7 values 6 months after the omalizumab treatment. This is similar to results reported in studies performed in other countries.

CSU exerts a significant impact on quality of life (2). Patients with CSU display sleep disorders, fatigue, and unpredictable disease duration in addition to angioedema and itching (26–30). Thomsen et al. reported that patients with CSU that were resistant to H_1 antihistamine treatment used healthcare services frequently and showed reduced quality of life (31). Maurer et al. reported a significant improvement in the quality of life of patients with CSU 12 weeks after omalizumab treatment, and Büyüköztürk et al. reported a significant improvement in the quality of life of patients with CSU 24 weeks after omalizumab treatment (21, 26). Savic et al. compared the effectiveness of omalizumab and cyclosporine treatments in patients with CSU and reported a significant improvement in the quality of life of patients receiving omalizumab treatment compared with that of patients receiving cyclosporine treatment (32). Consistent with those findings, the study presented here observed that DLQI scores markedly decreased and the quality of life of patients with CSU improved 6 months after omalizumab treatment. Moreover, 59.1% of patients did not require any other treatment concurrent with the omalizumab treatment. Omalizumab treatment decreases the daily requirement of antihistamines and immunosuppressive drugs, which may exert systemic side effects in the majority of patients, indicating that decreasing the need for additional medication may also improve the quality of life of patients with CSU. Furthermore, Nettis et al. reported that omalizumab is a good option for preventing polypharmacy in elderly patients (33).

To date, the clinical or laboratory data required to determine the effectiveness of omalizumab treatment has not been defined (6, 34–36). A study by Ghazanfar et al. involving 154 patients with chronic urticaria that were treated with omalizumab reported that the absence of angioedema, a negative result on a histamine release test, advanced age, a history of short-term disease, and no history of immunosuppressant use were positive determinants of a response to omalizumab treatment (12). In the study presented here, no statistically significant association was observed between treatment response and demographic data, disease-related parameters, or laboratory data 6 months after treatment.

Clinical studies have reported that upper respiratory tract infection, headache, and skin and subcutaneous tissue disorders

are the most common side effects of omalizumab treatment (37). Another study reported that the side-effect potential of omalizumab treatment was similar to that of placebo treatment (20). One clinical study reported a slight increase in sinusitis (4.9% vs. 2.1%), headache (6.1% vs. 2.9%), arthralgia (2.9% vs. 0.4%), and cough (2.2% vs. 1.2%) in patients receiving 300 mg omalizumab compared with those receiving placebo (7). In the present study, 89.4% of omalizumab-treated patients did not report any side effects; however, nausea was reported in 13 patients and myalgia in one patient. The decreased incidence of side effects after omalizumab treatment in this study may be because of underreporting in the medical records of the study patients.

The study presented here is valuable because it includes a large number of patients with CSU that were treated with 300 mg/month of omalizumab for 6 months, along with their detailed demographic and clinical data and UAS7 and DLQI values. However, the study had the following limitations: a) the number of patients continuing omalizumab treatment was unknown, b) changes in patient symptoms after the treatment was discontinued in the follow-up period were unclear, and c) the reasons for discontinuing treatment were not recorded.

In conclusion, these results indicate that treatment with 300 mg/month of omalizumab for 6 months is effective and safe for treating Turkish patients with recalcitrant CSU. Moreover, treatment efficacy was observed within the first 2 months after treatment in most patients. However, no significant association was observed between omalizumab treatment effectiveness and patient characteristics or disease-related parameters.

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