Original Article

Omalizumab in Chronic Urticaria; Real-life Data of 6-year-Experience

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Abstract

Background: Chronic urticaria (CU) is defined as the persistence of urticarial lesions for more than 6 weeks. Omalizumab, a human monoclonal anti IgE antibody, has been used as a new therapeutic option in CU patients unresponsive to high-dose second-generation antihistamines. **Aims and Objectives:** This study is aimed to examine the clinical and demographic characteristics of CU patients treated with omalizumab in our clinic and to define parameters related to therapeutic response. **Materials and Methods:** Patients who were followed up with the diagnosis of CU between January 2014 and June 2020 were evaluated retrospectively. The data obtained from patients' electronic files were analyzed using SPSS23 program. **Results:** 167 patients (125 female, 42 male) were included. The mean age was 45.34 ± 14.76 years. The mean disease duration at the onset of omalizumab was found to be 47.41 ± 63.26 months. Complete response to treatment was observed in 45.9%, 48%, and 52% of patients at 3rd, 6th, and 12th months of omalizumab treatment, respectively. The baseline total IgE level was evaluated in 107 patients and a statistically significant correlation was observed between complete response to treatment at 3rd month and higher baseline total IgE levels ($P < 0.001$). **Conclusion:** Omalizumab provided a significant therapeutic response and the patients did not need any other treatment, while patients with high pretreatment IgE levels showed a better and earlier response. These results may guide clinicians in predicting patients' response to omalizumab.

Keywords: Chronic spontaneous urticaria, chronic urticaria, inducible urticaria, omalizumab, treatment

Introduction

Urticaria is a skin disease characterized by itchy, erythematous, oedematous papules and plaques that appear suddenly and disappear spontaneously within 24 h. Angioedema might accompany to urticaria in a significant number of patients. Chronic urticaria (CU) is defined as the persistence of these urticarial lesions for more than 6 weeks. If symptoms occur without any external stimulus, it is classified as chronic spontaneous urticaria (CSU); if it occurs because of stimuli such as cold, heat, pressure, classified as chronic inducible urticaria (CIndU). In 10%–50% of patients, CSU occurs in combination with CIndU.[1,2]

Symptoms in CSU often last between one to five years (might continue for more than 5 years in 11%–14% of patients).[3] Second-generation H1 antihistamines are recommended as the first step in the treatment of CU and used up to 4 times in case of unresponsiveness, but even if the dose is increased, approximately 50% of patients do not respond.[4] Other therapeutic options frequently used are H2 antihistamines, leukotriene receptor antagonists, while systemic glucocorticoids are often used during acute urticarial flares. Omalizumab, which is a human monoclonal anti-IgE antibody and acts by reducing the level of free IgE and inhibiting mast cell and basophil activation, has been used as a new therapeutic option especially in CU in the last decade.[4] Omalizumab is recommended as the first treatment option in patients with CU unresponsive to high-dose second-generation antihistamines. It is generally used as 300 mg administered every 4 weeks. However, its effect is thought to be dose-dependent, so treatment

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response may vary in patients with different doses, thus the dose might be tailored according to the response.[5] The efficacy and safety of omalizumab in CSU treatment have been proven.[4] Omalizumab is also reported to be effective in CIndU such as cholinergic urticaria, cold urticaria, solar urticaria, symptomatic demographics, and late pressure urticaria. In addition, it increases the quality of life by reducing the development of angioedema and relapse after discontinuation of treatment in CU patients.[1,6] Other therapeutic options in resistant CU are cyclosporine, methotrexate, dapsone, hydroxychloroquine, and sulfasalazine, but data on the use of these treatments in CU are limited and these treatments can cause significant side effects.[7]

Materials and Methods

Patients who were followed up with the diagnosis of resistant CU between January 2014 and June 2020 in our clinic were retrospectively evaluated through the electronic patient files. Inclusion criteria of our study were patients who used omalizumab for at least 3 months, patients whose sociodemographic and clinical characteristics could be found from electronic patients' files. Data of patients with CSU with accompanying CIndU were also included in the study. Demographic data of the patients such as age, gender, duration of CU, history of CIndU, other accompanying diseases (autoimmune diseases, thyroid diseases, pernicious anemia, etc.), food or drug allergy, family history of urticaria or other allergic diseases (allergic rhinitis/conjunctivitis, allergic asthma, food allergy, drug allergy, etc.) were also scanned through the hospital records. In addition, the presence of accompanying angioedema was examined from the files in detail. Total serum IgE level, *Helicobacter pylori* antibody, Vitamin D, Vitamin B12, and thyroid hormone levels were retrospectively examined. Omalizumab dose and frequency of treatment and the effectiveness of treatment at 3rd, 6th, and 12th months were evaluated. Regarding the evaluation of therapeutic response to omalizumab, patients were divided into five groups; complete response to treatment (if there was no symptom and did not require the use of antihistamines), insufficiently controlled complete response (if occasional antihistamine use was present), partial response (if regularly using antihistamines), insufficient control (if needed systemic corticosteroids and/or cyclosporine in addition to regular antihistamines) and no significant improvement of complaints were accepted as unresponsiveness. Ethics approval was obtained from the Faculty of Medicine Clinical Research Ethics Committee (number: 70904504/459).

Statistical analysis

Data was analyzed using the SPSS 23 program. Descriptive statistics such as frequency distribution, mean, and standard deviation were used to define the sample. In cases where parametric test assumptions were not provided, "Mann–Whitney U" and "Kruskal–Wallis" tests were used. A 95% significance level (or $\alpha = 0.05$ margin of error) was used to determine the differences in the analysis.

Results

167 (125 [74.8%] female and 42 [25.2%] male) patients who received omalizumab treatment and met the inclusion criteria were included in the study, with a mean age of 45.3 ± 14.76 (age range: 17–86) years. The mean disease duration was 81.13 ± 69.86 (time range: 9–336) months. Sixty (56.1%) of them had a history of angioedema along with urticaria. Out of 80 patients whose history of CIndU was reached from patient files, 26 (32.5%) had both CSU + CIndU, while 54 (67.5%) only had CSU. Food allergy was found in 12 (15.4%) of 78 patients and drug allergy was detected in 15 (20%) patients out of 75 patients whom data was reachable from electronic files. Thyroid disease was detected in 20 (16.9%) of 118 patients. The sociodemographic characteristics of the patients are summarized in Table 1.

A total number of 152 (99.7%) patients had used antihistamines before omalizumab treatment. Since one patient had myasthenia graves, antihistamines could not be administered and omalizumab was started when urticaria could not be controlled with systemic corticosteroids. Systemic corticosteroids were used in 45 (49.15%) of the patients, whereas cyclosporine was used in 26 (30.2%) of them. Disease duration at the onset of omalizumab therapy was 47.41 ± 63.26 (range 1–300) months (n = 124 patients). The mean duration of omalizumab therapy was 12.64 ± 8.68 (range: 2–47) months (n = 148 patients). Complete response was observed in 68 (45.9%), 60 (48%), and 36 (52%) patients, respectively, at the 3rd, 6th, and 12th months of omalizumab therapy, and the response rates of omalizumab are summarized in Table 2. Treatment was discontinued in 120 (77.4%) patients, but relapse was observed in 86 (84.3%) of them with a period of 4.64 ± 5.43 months. When omalizumab was restarted, a good response was obtained in 66 (94.2%) patients, while 4 (5.71%) did not respond to treatment. 97 (85.6%) of the patients in our study were under control with treatment and remission without treatment was detected in 26 (24.3%) patients. There were 62 (54.9%) patients who are on omalizumab therapy during our data collection period. Baseline total IgE level was measured in 107 patients and found to have a mean value of 280.58 ± 361.81 IU/ml (mininimum: 1 and maximum: 2000). Higher baseline total IgE levels were detected in 67 (56.3%) patients. A statistically significant correlation was observed between discontinuation of omalizumab at the 3rd month and higher baseline total IgE levels ($P < 0.001$).

Discussion

Omalizumab is a human monoclonal antibody developed against IgE, acting by binding to free IgE in serum

Table 1: Sociodemographic and clinical characteristics of patients

Parameters (number of patients with data in electronic patient files)	Results, *n* (%)
Sex (*n*=167) (female/male)	42 (25.2)/125 (74.8)
Age (*n*=167)	45.34±14.76 (range:17–86)
Duration of disease (months) (*n*=167)	81.13±69.86
CU (*n*=80)	
CSU	54 (67.5)
CSU + CIndU	26 (32.5)
Concomitant diseases	
Angioedema (*n*=167)	60 (56.1)
Food allergy (*n*=78)	12 (15.4)
Drug allergy (*n*=75)	15 (20.0)
Allergic rhinitis/conjunctivitis (*n*=85)	18 (21.2)
Allergic asthma (*n*=73)	15 (20.5)
Thyroid diseases (*n*=118)	20 (16.9)
Anemia (*n*=126)	28 (22.2)
Vitamin D deficiency (*n*=62)	49 (79.0)
Vitamin B12 deficiency (*n*=61)	13 (21.0)
Autoimmune diseases (*n*=67)	8 (11.9)
Connective tissue disorders (*n*=65)	3 (4.6)
Total IgE levels	
Elevated IgE levels (*n*=119)	67 (56.3)
Mean value (*n*=107)	280.58±361.81
Treatment	
Antihistamines (*n*=153)	152 (99.3)
Systemic steroids (*n*=91)	45 (49.5)
Cyclosporine (*n*=86)	20 (30.2)

CU: Chronic urticaria, CSU: Chronic spontaneous urticaria, CIndU: Chronic inducible urticaria

Table 2: Response rates of omalizumab treatment according to different time frames

Response to omalizumab (number of patients evaluated)*	3rd month (*n*=148), *n* (%)	6th month (*n*=125), *n* (%)	12thmonth (*n*=69), *n* (%)
Complete response	68 (45.9)	60 (48.0)	36 (52.2)
Insufficiently controlled complete response	49 (33.1)	43 (34.4)	24 (34.8)
Partial response	20 (13.5)	16 (12.8)	4 (5.8)
Insufficient control	9 (6.1)	6 (4.8)	3 (4.3)
Unresponsiveness	2 (1.4)	0	2 (2.8)

*Complete response:If there was no symptom and did not require the use of antihistamines, insufficiently controlled complete response: If occasional antihistamine use was present, partial response: If regularly using antihistamines, Insufficient control: If taking systemic corticosteroids in addition to regular antihistamines, Unresponsiveness: No significant improvement in complaints

and preventing it from binding to FcεRI on mast cells and basophils. It reduces both the free IgE level and the number of receptors and prevents mast cell activation.[8] The efficacy and safety of omalizumab in CU have been demonstrated in placebo-controlled studies, but real-life data are limited. Maurer *et al*. revealed that omalizumab reduced symptoms in patients with CSU resistant to H1 antihistamines in their placebo-controlled randomized phase-3 studies.[9] In another study, the effectiveness of omalizumab was evaluated retrospectively in patients with CSU and CIndU, and it was concluded that omalizumab acts fast with high efficacy and safety in both groups.[10] Our results also showed 32.5% of patients had both CSU + CIndU, while 54 (67.5%) only had CSU. This was similar to the study by Maurer *et al*. in which no identifiable trigger factors for the symptoms were present in a large proportion of affected subjects.[11] Furthermore, in our study, omalizumab had a good therapeutic effect in both patients with CSU + CIndUand with CSU only, and no significant difference was found in terms of age, sex, the duration of omalizumab therapy, and the duration of relapse time after omalizumab discontinuation. However, relapses after omalizumab cessation were significantly more common in patients with CSU + CIndU ($P = 0.021$) than in CSU only ($P = 0.009$) and complete remission without any therapy was significantly higher in patients with CSU only.

In a recent study by Chen *et al*., a total of 138 patients (87 with CSU alone, 33 with different forms of CIndU, and 18

Table 3: Literature data regarding IgE levels and therapeutic response to omalizumab

Studies/year	Number of patients	Mean IgE levels (parameter)	Response rate, *n* (%)	IgE level after therapy	Relapse rate	Is total IgE a good marker of response?
Marzano *et al*.[5]/2019	470	Responders: 131.6 (507) KUA/L	425 (90.4)	-	First relapse: 60.2%-Second relapse: 66.3%**	Yes
		Non responders:42.1 (299) KUA/L*	45 (9.6)			
Metz *et al*.[10]/2014	44	CR: 110 (7–1667) KUA/L***	CR: 35 (79.54)	-	-	No
		PR or NR: 111 (5–882) KUA/L	PR+ NR: 9 (20.45)			
Nettis *et al*.[14]/2018	322	231.4 ± 506.6 KUA/L	4th week: 188 (58.4)	-	40.8%	Yes
			12th week: 232 (73.4)			
			20th week: 255 (84.2)			
			40th week: 107 (61.8)			
Ertaş *et al*.[20]/2018****	113	CR: 73.7 (19.5–153.8) IU/ml	43 (38.1)	CR: 290.5 (121.5–637.5) IU/ml	-	Yes
		PR: 82.0 (46.2–126.5) IU/ml	55 (48.6)	PR: 298 (205.8–543.5) IU/ml		
		NR: 17.9 (17.0–55.0) IU/ml	15 (13.3)	NR: 17.9 (17.4–86.2) IU/ml		
Cugno *et al*.[21]/2018	25	CR: 148 ± 114 KUA/L	-	-	-	Yes
		PR: 115 ± 432 KUA/L				
		NR: 16 ± 24 KUA/L				
Salman *et al*.[22]/2019	72	Group 1: 205.4±368.4 (9-2284) IU/ml*****	-	-	-	Yes
		Group 2: 261.2 ± 459.1 (0-1446) IU/ml				
Straesser *et al*.[24]/2018	137	1st quartile: 0–15.2 IU/ml†	48.4%	-	-	Yes
		2nd quartile: 15.3–68.8 IU/ml	86.1%			
		3rd quartile: 68.9–168.0 IU/ml	88.2%			
		4th quartile: 168.1–4261 IU/ml	94.1%			
Deza *et al*.[25]/2017	47	Responders: 151 (66–311) KUA/L	38 (80.9)	-	-	Yes
		Non responders: 20 (5–59) KUA/L	9 (19.1)			
Weller *et al*.[26]/2018‡	85	CR: 204.0IU/ml, (113.8-437.5)	43 (50.5)	-	-	Yes
		PR: 56.7IU/ml, (9.9-242.0)	23 (27)			
		NR: 16.7IU/ml, (8.4-32.4)	19 (22.3)			
Asero *et al*.[27]/2019§	76	Responders:183.5 KUA/L(87-372)	62 (81.5)	-	-	Yes (in non-atopic patients)
		Non responders: 58.5 KUA/L(8-452)	14 (18.5)			
Çildağ *et al*.[28]/2018‖	41	152 (42–444) mg/dl	CR:17 (41.4)	386 (159–1282) mg/dl	-	No
			SI: 21 (51.2)			
			NSI: 3 (7.3)			

Table 3: Continued

Studies/year	Number of patients	Mean IgE levels (parameter)	Response rate, *n* (%)	IgE level after therapy	Relapse rate	Is total IgE a good marker of response?
Magen *et al*.[29]/2019	106	CR: 146 ± 94 IU/ml PR: 159 ± 72 IU/ml NR: 109 ± 85 IU/ml	CR: 63 (58.9) PR: 27 (27.2) NR: 16 (14.9)	-	-	No

*Non-responder: Defined as a <30% reduction of UAS7 or an exacerbation at week 12, **In this study authors described first (within 2 months after first 24 weeks omalizumab treatment course) and second relapse (within 3 months after second 20 weeks omalizumab treatment course), ***KUA/L: Kilo Units per litre, Measurement of serum IgE levels according to the manufacturer's instructions (ImmunoCAP; ThermoFisher, Uppsala, Sweden), ****Patients with IgE levels that exceeded the upper assessment limit (1100 IU/ml) were excluded from analyses (*n*=17), *****Patients divided into two groups according to omalizumab dose; Group 1 includes patients with omalizumab 300 mg/4w and group 2 includes patients with omalizumab 450 mg/4w, †Subdivided into quartiles according to IgE levels, ‡Complete response (CR), partial (PR) and non-response (NR) was defined as the reduction of signs and symptoms by ≥90%, by ≥30% but <90%, and by <30% (physicians' global assessment), respectively, after 2 four-weekly injections of omalizumab 300 mg, §Nonresponse to omalizumab was defined as the absence of any change (i.e., >20%) in UAS-7 values 3 months after the start of the treatment. A fast response to omalizumab was defined as the disappearance or a reduction >50% of the UAS-7 score within 4 weeks after the first administration. A response was defined as slow if it occurred within 1 and 3 months after the first administration of the drug,‖"Complete response" to omalizumab was defined as a reduction of 90% or more in the UAS-7, a "significant improvement" as a reduction in the UAS-7 of 90% – 30% and "no significant improvement" as less than 30% reduction in the UAS-7. CR: Complete responders, PR: Partial responders, NR: Nonresponders; SI: Significant improvement, NSI: Not any significant improvement. UAS-7: Urticaria Activity Score-7

with both) were retrospectively examined. The response to omalizumab therapy were 86.2% in CSU alone (*n* = 75), 90.9% in CIndU (*n* = 30) and 83.3% in CSU + CindU (*n* = 15) and the speed of onset of omalizumab effect was comparable among patients with CSU, CIndU or both. However, complete response (defined by Urticaria Control Test = 16 during the period of treatment with omalizumab, with/without H1-antihistamine therapy) rate in patients with CSU only (69.0%, *n* = 60/87) or CIndU only (72.7%, *n* = 24/33) were significantly higher (*P* = 0.009) than that of patients with both CSU + CIndU (33.3%, *n* = 6/18).[1] Moreover, Türk *et al*. showed that comorbidity of CindU was linked to longer disease duration and higher disease activity.[2] Thus, it is important to document triggering factors and inducible urticaria if it accompanies to CSU.

Our study demonstrated high response (including complete response, insufficiently controlled complete response, and partial response) rate of 92.5% at the 3rd month and 92.8% at the 12th month of omalizumab therapy. However, we could not evaluate response with urticarial control test (UCT) due to retrospective design and lack of data. A recent meta-analysis of real-world data including 45 studies reported an average complete response rate of 72.2% and an average partial response rate of 17.8% for CSU.[12]

In CU, grouping patients according to omalizumab therapeutic response and revealing clinical and laboratory parameters that will predict the response may facilitate better management of CU. In several studies, the indicators of good response to omalizumab therapy in CSU were reported as the absence of angioedema, negative histamine release test, advanced age, short disease duration, no history of systemic immunosuppressive therapy, higher levels of total IgE, a reduction of plasmatic D-dimer and serum IL-31 levels, higher expression of FceRI and the absence of serum stimulating activity of expression of CD203c on basophils.[13-16] On the other hand, a positive basophil histamine release assay (BHRA), a positive autologous serum skin test, and the presence of eosinopenia are shown to predict a slow or poor response.[15-17]

Delineation of different categories of responders to omalizumab as well as the investigation of both biological and clinical markers predictive of response to omalizumab could ameliorate the management of CSU patients.[5] Elevated IgE levels in patients with CU have been noted previously.[18] In a study, Kessel *et al*. showed that one-third of patients with CU had significantly elevated levels of total IgE compared with the control group. In addition, they found 93% of CU patients with elevated IgE had moderate to severe urticaria.[19]

In a prospective study, Ertaş *et al*. evaluated if response rates to treatment with omalizumab in patients with CSU are linked to their baseline IgE levels, their IgE levels after omalizumab treatment, and the ratio of on treatment IgE/baseline IgE levels [Table 3]. They found nonresponders to omalizumab had significantly lower baseline IgE levels than partial responders and complete responders. After 4 weeks of omalizumab treatment, non-responders have lower total IgE levels than responders. As a result, authors suggested IgE levels of CSU patients and their change can predict the outcome of omalizumab treatment.[20] Similarly, in other studies, initially high IgE level was associated with good treatment response as seen in our results.[5,21-23] Similar findings were reported by Straesser *et al*. (*n* = 137, CSU patients) retrospectively and they observed an association between the lack of serum IgE and a lower likelihood of omalizumab response. They also subdivided serum IgE levels into quartiles and response to omalizumab differed significantly according to quartiles. A low baseline serum IgE ≤15.2 IU/mL was shown to predict a lower likelihood of response to omalizumab.[24] In a retrospective study of 332 CSU patients, Nettis *et al*.

showed that higher pretreatment IgE levels (above 48 KUA/L) were significantly less likely to be associated with a Urticaria Activity Score-7day (UAS7) score > 6 (non-responders) at the end of the 24-week treatment period. They also reported that cyclosporine use, angioedema history, and duration of CSU were also associated with nonresponder group.[14]

Marzano *et al*. reported that baseline IgE correlated to a good response to omalizumab since levels were significantly higher in responders than nonresponders. Among responders, there was no significant difference in terms of clinical response categories, namely early complete responders (the disappearance of symptoms within 1 week from the start of omalizumab), late complete responders (disappearance of symptoms within 12 weeks from omalizumab starting), and late partial responders (defined as an at least 30% reduction of UAS7 as compared to baseline, evaluated at week 12).[5] Although a relationship was found between the length of the disease duration and the development of primary and secondary relapse in the same study, a similar relationship was not observed in our study. In their study, Marzano *et al*. found female gender associated with treatment unresponsiveness.[5] However, no relationship was found between gender and therapeutic response in our study.

In a prospective study, Deza *et al*. investigated immunological predictors of response to omalizumab therapy.[25] They reported responders (defined as an improvement in the patients' signs and symptoms achieving UAS7≤ 6 or ≥90% reduction in the UAS7 at 6 months of treatment) showed higher baseline total IgE levels in comparison with nonresponders but authors implied that there is not enough argument to believe in the assessment of total IgE as a good therapeutic predictor in CSU. This is due to the wide range (and therefore overlap) of IgE values observed in responders (16–683 kU/l) and nonresponders (1–100 kU/l).[25] Weller *et al*. showed notably elevated IgE levels in the majority (77. 5%) of CR, in 31.8% of PR and only in 20.0% of NR. They emphasized elevated total IgE levels were common in CR and only rarely detectable in NR to omalizumab. Normal and particularly low normal total IgE levels were prevalent in NR and only rarely detectable in CR. However, normal and low total IgE levels were found in all responder types as a result authors suggested total IgE levels cannot be used as a stand-alone predictor of response to omalizumab.[26]

In a small study population, Cugno *et al*. also found nonresponders have significantly lower baseline IgE levels than partial and complete responders.[21] Since the atopic status is often associated with elevated levels of total IgE, in an exploratory study by Asero *et al*., evaluated the role of atopic status in modifying the predictive value of total IgE levels. When total IgE was analyzed, omalizumab responders and nonresponders did not differ significantly regarding the baseline levels. However, if atopic patients were excluded from the analysis, omalizumab responders showed much higher total IgE levels than nonresponders.[27] Authors implied analyzing the atopic status of CSU patients is important because atopic status acts as a factor modifying the ability of total IgE levels in predicting the response to omalizumab. In the same study, within the responders' group, fast responders showed much higher mean total IgE levels than slow responders.[27] However, they suggested that one should be cautious to accept this laboratory parameter as a predictive factor of response because several CSU patients with high total IgE levels are also nonresponders to omalizumab.

Çildağ *et al*. could found no significant differences in baseline IgE levels between patients with a complete response and without ones.[28] Magen *et al*. reported higher levels of total IgE in patients with CSU with partial responders to omalizumab than nonresponders, but this was not statistically significant, maybe due to the small number of patients in their study.[29]

Similarly, two retrospective studies by Metz *et al*. and Viswanathan *et al*. did not show significant differences in serum IgE concentrations between omalizumab responders and nonresponders.[10,30] Hence, there are conflicting results about baseline IgE level and its predictive role in omalizumab treatment response in the literature [Table 3]. We observed a statistically significant correlation between discontinuation of omalizumab at the 3rd month and higher baseline total IgE levels ($P < 0.001$) and this result was compatible with previous literature.

In a prospective study, increased serum total IgE levels are linked to faster relapse of CSU after discontinuation of omalizumab.[23] However, we found no significant relationship between the relapse time after omalizumab discontinuation and the baseline IgE level. In our study, 84.3% of the patients had relapses in an average of 4.64 months with omalizumab discontinuation; however, when omalizumab restarted again, the treatment was effective in 94.2% of the patients. This result was consistent with other studies in the previous literature.[10,31]

Complete response rates for omalizumab treatment were 45.9% at 3rd month, 48% at 6th month, and 52.2% at 12th month in our study. The complete response rates in the 3rd month of our study were found to be higher than ASTERIA I (44%), ASTERIA II (35.8%), and GLACIAL (34%), which are randomized phase-3 studies involving groups using omalizumab with a dose of 300 mg/month.[9,32,33] Data on the long-term use of omalizumab in CU are limited, and in the randomized placebo-controlled XTEND-CIndU study, patients were followed for a 48-week treatment period and showed evidence for the benefits of regular use of omalizumab to prevent recurrence of symptoms and sustainable disease control. In addition, it was stated that real-life data on long-term use of

omalizumab are needed.[34] Har *et al*. evaluated 10 patients with persistent CU who had been using omalizumab for more than 1 year; they recommend that omalizumab is effective and safe in the use of more than 1 year and that the spontaneous remission status should be evaluated by discontinuing the treatment from time to time.[35] This may be related to omalizumab reducing FcεRI levels on mast cells and basophils in 12–16 weeks by acting on free IgE.[36] In the study of Kaplan *et al*., patients were divided into two groups according to omalizumab therapeutic response as early responders (those who respond in the first 4–6 weeks) and late responders (those who respond in 12–16 weeks). Terminating the treatment before the 12th week causes a group of patients who will respond to the treatment to miss this opportunity. In addition, a response may occur after 24 weeks in late responders and may be observed within the first week in early responders.[37] In a study that retrospectively evaluated the effectiveness of omalizumab in 110 patients, complete response or significant improvement was achieved at a rate of 80.8% and disease control was achieved in 60% without the need for any other medication. In this study, omalizumab was discontinued in 37.3% of the patients due to complete remission but relapse occurred in 47.5% of them and when omalizumab was restarted and a complete response was obtained again at a rate of 90%.[38] However, different therapeutic protocols were used and therapeutic responses by specific time points were not determined.[38] In our study, omalizumab was discontinued at a higher rate (n = 120, 77.4%) and relapse rate was also higher (86 [84.3%]). When omalizumab was restarted, a good response was obtained in 66 (94.2%) patients, while 4 (5.71%) did not respond to treatment. Therefore, it was observed that the effect did not decrease when omalizumab was restarted in our study.

In our study, accompanying thyroid disease was found in 20 patients (16.9%). This result was consistent with previous studies,[31,39,40] which reflects autoimmune characteristics of both diseases. The angioedema was detected in 60 (56.1%) patients. This was in line with the study of Maurer *et al*. in which 58.5% (394 of 673) of patients had CSU-associated angioedema.[11] Although Ghazanfar *et al*. observed that the absence of concomitant angioedema was associated with a good omalizumab response,[13] no relationship was found between therapeutic response and the presence of angioedema in our study. In addition, it has been reported that the 300 mg/monthly dose of omalizumab is effective in controlling angioedema.[9]

In our study, the duration of omalizumab use in patients with a history of triggering medication was found to be significantly shorter (24.12 months) than those without it (39.73 months) (P = 0.016). Various drugs can trigger the development of CU through nonallergic hypersensitivity.[4] Therefore, when a triggering drug is detected, its use should be discontinued. Furthermore, in our study, the time between discontinuation of omalizumab and relapse was shorter than those without a history of food allergy (17.5 months; 26.3 months, respectively), but this value was not statistically significant (P = 0.059). It is extremely rare for an IgE-mediated food allergy to cause CU. If the nutrient relationship is detected and eliminated, the symptoms regress within 24 h. No other study was found in the literature comparing the triggering drug with the duration of omalizumab use and the relationship between food allergy and relapse. Thus, this relationship needs to be further investigated. Following omalizumab discontinuation, patients usually relapse within a few months, while rapid remission occurs when omalizumab is started again. Higher baseline IgE levels have been associated with faster relapse following omalizumab discontinuation.[23] In addition, baseline UAS7 was significantly correlated with the risk of developing first relapse but not the second one.[5] As far as we know, there is no other marker that indicates when and which patient relapses after discontinuation of treatment.

Omalizumab was generally well tolerated in the study group, with tachycardia observed in only one patient. Our study was limited by its retrospective nature and being a small sample, which might limit the breadth of our analysis. In addition, data retrieval also represented a possible limitation in our study as in some cases we could not reach all the information from the medical chart.

Conclusion

Our study which is the real-life data of a tertiary center, omalizumab is a safe and effective therapeutic option in patients with CU who are unresponsive to antihistamines. Although there are some markers that will predict the treatment outcome, new studies are needed to reveal their validity. Furthermore, determining omalizumab response patterns may lead us to better understand the pathophysiology of the disease and to apply personalized treatments in future.

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Conflicts of interest

There is no conflict of interest nor financial support or sponsorship.

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