



## A patient-oriented approach to long-term use of omalizumab in chronic spontaneous urticaria

Sinem Ornek & Emek Kocaturk

To cite this article: Sinem Ornek & Emek Kocaturk (2021): A patient-oriented approach to long-term use of omalizumab in chronic spontaneous urticaria, Cutaneous and Ocular Toxicology, DOI: [10.1080/15569527.2021.1945618](https://doi.org/10.1080/15569527.2021.1945618)

To link to this article: <https://doi.org/10.1080/15569527.2021.1945618>



Published online: 02 Jul 2021.



Submit your article to this journal [↗](#)



Article views: 15



View related articles [↗](#)



View Crossmark data [↗](#)

RESEARCH ARTICLE



## A patient-oriented approach to long-term use of omalizumab in chronic spontaneous urticaria

Sinem Ornek<sup>a</sup> and Emek Kocaturk<sup>b</sup>

<sup>a</sup>Department of Dermatology, University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey;

<sup>b</sup>Department of Dermatology, Koc University School of Medicine, Istanbul, Turkey

### ABSTRACT

**Background:** Omalizumab is an effective and safe treatment for antihistamine resistant chronic spontaneous urticaria (CSU), however, long-term efficacy and safety remains unclear.

**Objective:** To evaluate the efficacy and safety of omalizumab in CSU patients treated for long term and to identify long-term management strategies.

**Methods:** We retrospectively analyzed demographic characteristics, clinical features, laboratory parameters and treatment outcomes of 41 CSU patients who received omalizumab for at least 3 years. Treatment responses were evaluated with urticaria control test (UCT). Treatment safety was evaluated by comparing laboratory findings before and three years after omalizumab initiation as well as considering patients' adverse event reports.

**Results:** The patients (mean age 40.46 years; 63.4% women) received omalizumab for an average of 41.93 months (mean 31.68 injections/patient). The mean baseline UCT score was 5.56 and average number of injections to reach UCT score  $\geq 12$  was 3.3. Nine patients (22%) responded insufficiently to 300 mg/4 weeks omalizumab and required up dosing. Thirty-eight patients (92.7%) could tolerate longer dose intervals ( $>4$  weeks) and the dose interval was increased after a mean of 11.53 injections. There was no loss of efficacy of omalizumab. Sixteen patients (39%) had been retreated with omalizumab after a mean discontinuation time of 24 weeks. Five patients (12.2%) reported mild and transient adverse effects. Liver and renal function tests as well as full blood count before and after omalizumab were in normal ranges.

**Conclusion:** For the long-term management of CSU, omalizumab is a safe and effective treatment which can be tailored according to patients' disease activity.

### ARTICLE HISTORY

Received 9 April 2021

Revised 27 May 2021

Accepted 11 June 2021

### KEYWORDS

Adverse events; efficacy; omalizumab; treatment; urticaria; long term; safety

### Introduction

Chronic urticaria (CU) is a disorder characterized by recurrent pruritic wheals and/or angioedema that persists over 6 weeks affecting up to 1% of the total population. It is classified as chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) depending on whether a specific trigger elicits the lesions or not<sup>1</sup>. CU may severely affect patients' quality of life; i.e. sleep, daily activities and social life<sup>2</sup>.

The EAACI/GA<sup>2</sup>LEN/EDF/WAO urticaria treatment guideline recommends starting with a standard dose of second-generation H1-antihistamine (sgAH) and then increasing the dose up to four folds in unresponsive cases. In patients recalcitrant to four-fold doses of sgAH, omalizumab 300 mg every 4 week is recommended as add-on therapy<sup>1</sup>.

Clinical trials (ASTERIA I, ASTERIA II and GLACIAL) and real-life studies showed that omalizumab is a very effective and safe treatment in patients with CSU resistant to sgAH<sup>3-7</sup>. Also, short-term and long-term omalizumab treatments have been well described as effective and safe in patients with asthma up to 121 months<sup>8,9</sup>. However, long-term results are not well documented for CSU in the literature. In the XTEND-

CIU study, the efficacy and safety of omalizumab in CSU patients have been evaluated during a 48-week and 60-week study periods, respectively. The results of this trial showed omalizumab is effective in preventing return of symptoms and safe for use, in one-year period<sup>10</sup>. Nevertheless, there is an unmet need to understand the real-life consequences of longer omalizumab treatment in CSU patients. We need this information because CSU lasts longer than one year in a significant proportion of patients<sup>11</sup> and these patients require longer omalizumab therapy to avoid relapses<sup>10</sup>.

Moreover, some CSU patients experience return of symptoms before 4 weeks with the recommended dose of omalizumab and require shorter intervals or higher doses<sup>12,13</sup>. It was also observed that some CSU patients who achieved remission but still needed maintenance doses might remain symptom-free for longer than 4 weeks with a single 300 mg dose of omalizumab<sup>14</sup>. These raise the questions of whether treatment regimen of patients receiving long-term omalizumab can be modified upon patients' symptoms, and, if so, whether the modified regimens will be as effective as the recommended treatment regimen.

In our study, we aimed to evaluate the efficacy and safety of omalizumab in CSU patients treated with omalizumab over a 3-year period and to identify long-term management strategies.

## Methods

### Study population

We performed a retrospective analysis of CSU patients who have been treated with omalizumab in Urticaria Centre of Reference and Excellence (UCARE)<sup>15</sup> of Okmeydanı Training and Research Hospital between January 2013 and July 2019. The patients who were treated with omalizumab longer than 3 years were included in the analysis. The patients with isolated CIndU and chronic episodic urticaria, patients whose disease activity and control scores were not specified at baseline, and those using omalizumab for less than 3 years were excluded from the study. Data regarding age, gender, duration of symptoms until omalizumab was started, existence of angioedema, accompanying CIndU, total IgE values, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and thyroid antibody levels, autologous serum skin test (ASST) results (if they exist in patients' file), accompanying comorbidities and concomitant treatments were noted.

### Assessment of disease activity

Baseline disease activity was assessed using in-clinic urticaria activity score (IC-UAS) which includes two questions including the number of hives (0, none; 3, >12) and severity of pruritus (0, none; 3, severe and difficult to tolerate) for last 24 h prior to the visit. The total score is calculated as a sum of components, and higher scores indicate higher disease activity<sup>16</sup>.

### Assessment of treatment outcome

Omalizumab and accompanying sgAH treatment were noted. Treatment response was assessed using the Urticaria Control Test (UCT) which includes four questions regarding the control of signs and symptoms of the disease, quality of life impairment, efficacy of treatment and overall disease control over the prior 4 weeks. The questions are rated from 0 to 4, and the total score is calculated by summing the four individual question scores. A score of  $\geq 12$  indicates well-controlled urticaria, while a score of  $\leq 11$  indicates poor disease control<sup>17,18</sup>. The week at which UCT score  $\geq 12$  was achieved after omalizumab treatment was also noted.

The dose intervals and doses of patients who received omalizumab at different intervals or doses from the recommended regimen were noted. The dose intervals of patients were determined using urticaria activity score summed over 7 days (UAS7) before injection. If there were any urticaria activity (UAS7 > 0) at the last week before injection, the intervals of patients were reduced to 2 weeks. If no urticaria activity is present (UAS7 = 0) at the last week before injection after 3 monthly injections, the dose intervals were increased

by 1-week in each visit (as long as UAS7 = 0 at the last week).

A gap of 16 weeks between two consecutive omalizumab injections accepted as "remission of disease" and led to "discontinuation of the drug." And patients, who were restarted on omalizumab after discontinuation, considered as "retreated." The treatment responses of retreated patients were also evaluated.

### The definitions of the groups whose characteristics were compared

Additionally, data included in the study were compared between the patient groups, which were defined as below:

- Patients who poorly responded to standard doses of omalizumab and needed higher doses (Oma<sup>H</sup>).
- Patients who well responded to standard doses of omalizumab (Oma<sup>S</sup>).
- Patients who respond to omalizumab before 12 weeks (quick responders).
- Patients who respond to omalizumab after 12 weeks (slow responders).

### Assessment of treatment safety

To evaluate the safety profile of omalizumab, adverse effects of omalizumab therapy reported by the patients were noted. Moreover, the laboratory findings before and three years after omalizumab were also noted and compared with baseline to assess whether anaemia, leukopenia and thrombocytopenia developed or liver and kidney functions were affected by the drug.

### Data analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.21.0. (IBM Corp., Armonk, NY). All investigated features of the study population were analyzed using descriptive statistics. Categorical variables were described with frequencies and percentages. Quantitative variables were presented as mean  $\pm$  standard deviation (SD) or median (range) as appropriate. The Kolmogorov–Smirnov test was used to decide the normality of the distribution of numeric variables. Independent samples *T* test or Mann–Whitney *U* test were used to compare numeric variables and Fisher's exact test was used to compare categorical variables between independent groups. Paired samples *T* test or Wilcoxon Signed-rank test were used to compare consecutive data including baseline and third year laboratory parameters, considering whether the variables are normally distributed or not. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. The level of statistical significance was accepted at  $p < 0.05$ .

This study was approved by the Ethics Committee of Okmeydanı Training and Research Hospital (number of IRB:

48670771–514.10). The participants gave written informed consent and patient anonymity was preserved using methods approved by the Ethics Committee.

## Results

### Patient characteristics, comorbidities and concomitant medications

The study enrolled 41 patients who were treated with omalizumab over a period of at least 3 years (10.5% of all omalizumab treated CSU patients). For demographic, clinic and laboratory data, see Table 1.

The most common comorbidity was found as atopic disorders (19.5%). All comorbidities of the patients and concomitant medications are reported in Table 2.

### Data on treatment

Treatment data regarding omalizumab and accompanying sgAH are summarized in Table 3. The mean duration of omalizumab treatment was  $41.93 \pm 6.54$  months with a median of 38 months (range 36–62 months). Average number of omalizumab administrations was  $31.68 \pm 9.9$  injections per patient with a median of 32 injections (range 13–62 injections). While 37 patients (90.2%) continued to receive omalizumab therapy, 4 patients (9.8%) discontinued after symptoms relieved in a mean time of 41 months. Thirty-seven patients (90.2%) achieved UCT score  $\geq 12$  in less than 12 weeks (quick responders). Four patients (9.8%) achieved UCT score  $\geq 12$  after 12 weeks (slow responders).

Of all, 9 patients (22%) responded insufficiently to 300 mg/4 week omalizumab therapy and they required up dosing of omalizumab either with 300 mg every 2-weeks or 600 mg at 4-week intervals (Oma<sup>H</sup> patients). In the follow-up period after the symptoms of these patients relieved, omalizumab was continued with the standard interval (300 mg/4 week) in 2 of them (22.2%) while dose intervals have been increased

to more than 4 weeks in 6 patients (66.7%). One patient (11.1%) was still on 300 mg/2 weeks of dose regimen.

There were no significant differences in demographic characteristics, clinical features, baseline disease severity and laboratory parameters between patients who needed higher doses of omalizumab or not (Oma<sup>H</sup> versus Oma<sup>S</sup>,  $p > 0.05$ ). Also, these parameters did not differ between slow responders and quick responders ( $p > 0.05$ ). However, late responsiveness was found to be positively correlated with requirement of higher doses of omalizumab ( $r = 0.620$ ,  $p < 0.001$ ).

In 38 patients (92.7%), the dose interval of omalizumab was increased after a mean of  $11.53 \pm 8.58$  injections (range 3–38 weeks; median: 8 weeks). In 28 of them (73.7%), the dose interval of omalizumab was increased in the first year. At the final evaluation, intervals of the patients who tolerated longer intervals were ranging from 4 to 14 weeks with a median of 7 weeks. Only in three patients (7.3%), the dose intervals could not be extended to more than 4 weeks. In case of exacerbations of CU symptoms, the dose intervals of the patients, who have been treated with increased intervals, had been decreased again as seen in Figure 1. There was no loss of efficacy reported by the patients.

**Table 2.** Comorbidities of the patients and concomitant medications.

| N = 41                                                    |                         |
|-----------------------------------------------------------|-------------------------|
| Comorbidities of patients, n                              | Concomitant medications |
| Atopic disorders                                          |                         |
| Asthma, 5                                                 |                         |
| Allergic rhinitis, 2                                      |                         |
| Penicillin hypersensitivity, 1                            |                         |
| Hypertension, 3                                           | Antihypertensive        |
| Hypercholesterolemia, 2                                   |                         |
| Gastritis, 2                                              | Proton pump inhibitors  |
| Migraine, 2                                               | Eletriptan              |
| Thyroid disease, 2                                        | Levothyroxine           |
| Behçet's disease, 1                                       | Colchicine              |
| Myocardial infarction, 1                                  |                         |
| Diabetes mellitus, 1                                      | Insulin                 |
| Others (Anxiety disorder, Benign prostate hyperplasia), 2 | Sertraline, Doxazosin   |

**Table 1.** Demographic, clinic and laboratory characteristics of the patients.

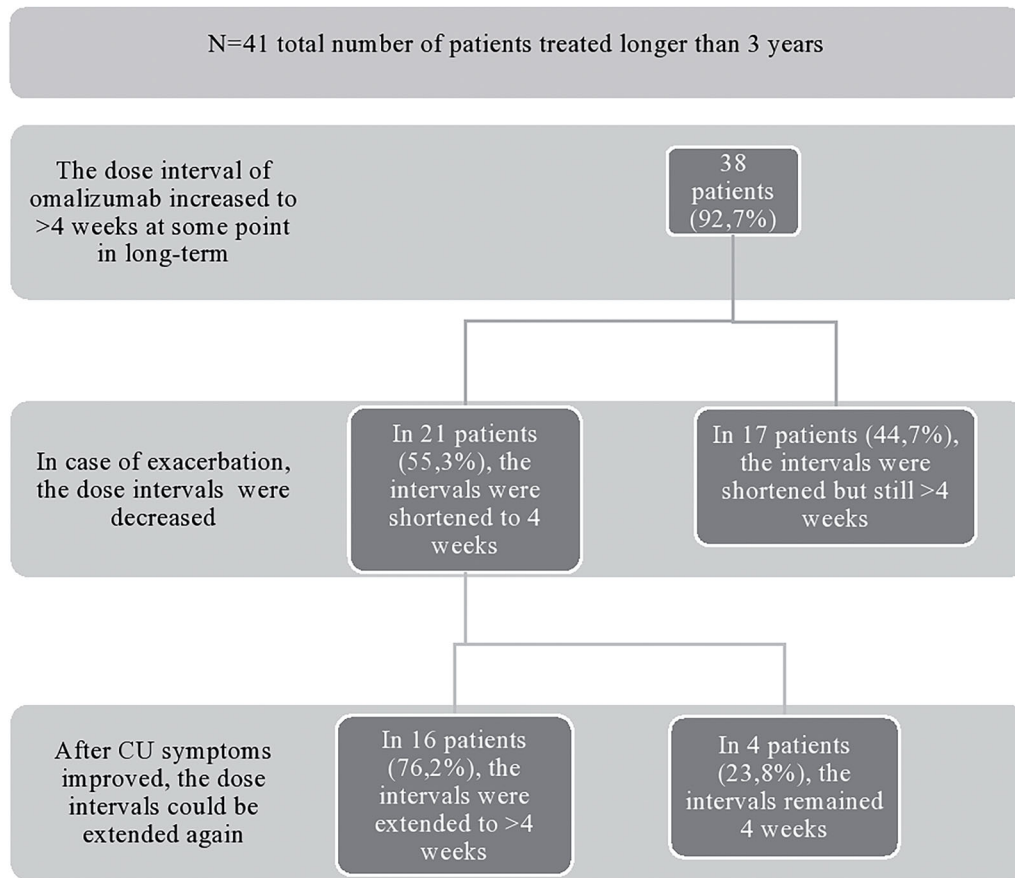
| Characteristics                                                                       | N = 41                           |
|---------------------------------------------------------------------------------------|----------------------------------|
| Age (year), mean $\pm$ SD; min–max                                                    | 40.46 $\pm$ 10.14; 23–63         |
| Gender; female, n (%)                                                                 | 26 (63.4)                        |
| Duration of CU symptoms to omalizumab initiation (mo), mean $\pm$ SD; median; min–max | 53.56 $\pm$ 85.19; 30; 3–480     |
| Presence of angioedema, n (%)                                                         | 27 (65.9)                        |
| Concurrent CINDU, n (%)                                                               | 19 (46.3)                        |
| Symptomatic dermatographism                                                           | 10 (24.4)                        |
| Cholinergic urticaria                                                                 | 6 (14.6)                         |
| Delayed pressure urticaria                                                            | 4 (9.8)                          |
| Cold urticaria                                                                        | 2 (4.9)                          |
| In-clinic UAS score (pre-oma)                                                         |                                  |
| Wheal score, mean $\pm$ SD; min–max                                                   | 1.7 $\pm$ 1.18; 0–3              |
| Pruritus score, mean $\pm$ SD; min–max                                                | 1.9 $\pm$ 1.1; 0–3               |
| Total score, mean $\pm$ SD; min–max                                                   | 3.5 $\pm$ 1.9; 0–6               |
| Baseline UCT scores (pre-oma), mean $\pm$ SD; min–max                                 | 5.56 $\pm$ 2.9; 0–10             |
| Total IgE values (IU/mL), N = 38; mean $\pm$ SD; median; min–max                      | 486.92 $\pm$ 604.4; 235; 20–2500 |
| Increased ESR levels, N = 28; n (%)                                                   | 4 (14.3)                         |
| Increased CRP levels, N = 28; n (%)                                                   | 10 (35.7)                        |
| Increased antiTPO levels, N = 27; n (%)                                               | 6 (22.2)                         |
| Increased antiTG levels, N = 27; n (%)                                                | 4 (14.8)                         |
| ASST positivity, N = 24; n (%)                                                        | 10 (41.7%)                       |

Anti-TG: Anti-thyroglobulin antibody; Anti-TPO: anti-thyroid peroxidase antibody; autologous serum skin test (ASST); CINDU: chronic inducible urticaria; CU: chronic urticaria; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IC-UAS: in-clinic urticaria activity score; UAS: urticaria activity score; UCT: urticaria control test.

**Table 3.** Treatment data on omalizumab and accompanying sgAH treatment.

| General treatment data                                                                                       | N = 41                      |
|--------------------------------------------------------------------------------------------------------------|-----------------------------|
| Duration of omalizumab treatment (mo), mean $\pm$ SD; median; min–max                                        | 41.93 $\pm$ 6.54; 38; 36–62 |
| Total number of omalizumab injections, mean $\pm$ SD; median; min–max                                        | 31.68 $\pm$ 9.9; 32; 13–62  |
| Usage of sgAH along with omalizumab, n (%)                                                                   | 28 (68.3)                   |
| UCT score $\geq$ 12 has been achieved at first three doses, n (%)                                            | 29 (70.7)                   |
| UCT score $\geq$ 12 has been achieved at first dose, n (%)                                                   | 14 (34.1)                   |
| Slow response to omalizumab (>12 weeks), n (%)                                                               | 4 (9.8)                     |
| Number of omalizumab injections to reach UCT score $\geq$ 12, mean $\pm$ SD; median; min–max                 | 3.32 $\pm$ 3.52; 3; 1–19    |
| Modification of dose regimen, n (%)                                                                          |                             |
| Updosing omalizumab (300 mg/2 weeks or 600 mg/4 weeks), n (%)                                                | 9 (22)                      |
| Increasing dose interval, n (%)                                                                              | 38 (92.7)                   |
| Number of standard dose omalizumab injections until increasing dose interval, mean $\pm$ SD; median; min–max | 11.53 $\pm$ 8.58; 8; 3–38   |

sgAH: second-generation H1-antihistamine; UCT: urticaria control test.

**Figure 1.** The modification of dose intervals according to the activity of the disease.

Sixteen patients (39%) had been retreated with omalizumab after a mean discontinuation time of 24 weeks. Eleven of them (68.6%) interrupted omalizumab treatment themselves without consulting to their physicians, of whom 90.9% were in quick responder group. While 5 of these patients had uncontrolled disease (UCT < 12) when they stopped their treatment, 7 were under control (UCT  $\geq$  12) with omalizumab. Four of retreated patients (25%) had discontinued their treatment after improvement under our supervision. One patient (6.3%) had discontinued because of unresponsiveness to standard regimen, but after a failure of a period of cyclosporine therapy the patient was retreated with higher dose of omalizumab with success. Of retreated patients, 12 (75%) achieved UCT  $\geq$  12 at the first dose while average doses to

reach this score was  $3.44 \pm 6.98$  doses in all retreated patients with a median of 1 dose (range 1–29 doses).

#### Adverse events and long-term safety of omalizumab

Five patients (12.2%) reported adverse effects that might be related to omalizumab, including injection-site reactions, hair loss, malaise, menstrual irregularity and motion disability on hand joints. Anaphylaxis was not reported.

The laboratory findings consisting of liver and renal function tests and full blood count were in normal ranges both before and after omalizumab treatment. The statistical difference was found only between aspartate dehydrogenase (AST) levels ( $p = 0.019$ ) which the levels after omalizumab

treatment were slightly increased but still in normal ranges. There was no statistical difference between haemoglobin, leukocyte, platelet counts, blood urea nitrogen, creatinine, and alanine dehydrogenase (ALT) levels before and after treatment ( $p > 0.05$ ).

## Discussion

This study is an observational study over a period of 6 years based on real life experiences in a UCARE<sup>15</sup> Centre. Of the CSU patients who were treated with omalizumab in our centre, 10.5% required continuous use of omalizumab for longer than 3 years.

The clinical course of CU varies among patients and it persists over 1 year in more than 70% of the cases and still exists in 14% after 5 years<sup>11</sup>. The mean duration of CU symptoms until omalizumab initiation was around 5 years in our study and one case had persistence of symptoms over 20 years. These observations support the results of the XTEND-CIU study, which suggested that patients should be treated for longer than 48 weeks<sup>10</sup>. Omalizumab does not change the clinical course of CU, but relieve effectively the symptoms of CU in sgAH resistant patients<sup>4,7,10,11,19,20</sup>. In our study, the symptoms of all patients have been controlled with omalizumab and some needed concomitant sgAH treatment. There were no patients who discontinued omalizumab treatment due to loss of efficacy. These findings indicate that omalizumab can be used for longer periods without losing its effect.

In several studies, it was shown that omalizumab provides rapid onset of symptom control<sup>14,19,21–23</sup>. Similarly, the symptoms of the majority were controlled in the first three treatments in our study (70.7%) (Table 3). On the other hand, the minority (12%) responded after 24 weeks. Kaplan et al.<sup>24</sup> analyzed the response patterns of omalizumab in CU and they showed that patients who have not responded after 12 weeks may still respond after 24 weeks, which is compatible with our results. Currently, the exact mechanism underlying late responders remains unclear and it is not established why some patients respond rapidly while others take longer to respond<sup>24</sup>. Gericke et al.<sup>25</sup> found that BHRA (basophil histamine release assay)-positive and ASST-positive CU patients were more likely to have a slow response to omalizumab compared with BHRA-negative and ASST-negative patients. Similarly, Nettis et al.<sup>26</sup> also identified a significant association between ASST positivity and slower response to omalizumab in CSU patients. In our study, we did not find an association between autoimmunity and late responsiveness to omalizumab, but this result may be misleading due to the low number of late responders in the study population. On the other hand, we observed that standard dose regimen of omalizumab was insufficient in all slow responders and they required up dosing to 600 mg (either 300 mg/2 weeks or 600 mg/4 weeks).

Consistent with the guideline, omalizumab was given as add-on therapy to all patients at the beginning. But in course of time, 68.3% of our patients continued to use sgAH along with omalizumab while others discontinued. Similar to ours, another study reported concurrent use of sgAH with

omalizumab in 61.1% of CSU patients and another study confirmed the efficacy of sgAHs for the treatment of the intermittent symptoms in patients with well-controlled urticaria under omalizumab treatment<sup>22,27</sup>.

In this study, all patients were initiated omalizumab on the recommended dose and intervals (300 mg/4 weeks). However, an individualized approach was performed in most of the patients, and the dose or the dose intervals were adjusted according to the changes in disease activity in each visit. Some patients did not tolerate 4-week dosing intervals and experience return of symptoms before 4 weeks; then were treated with 150 mg/2 weeks. In this group of patients, implementation of 150 mg of omalizumab at 2-week intervals has been shown to provide symptom control<sup>12</sup>. On the other hand, some patients might require higher doses of omalizumab to have control. Up dosing of omalizumab (either by increasing the dose or by shortening the dose interval, i.e. 600 mg in 4-week intervals or 300 mg in 2-week intervals) has been reported to be effective in a proportion of patients who remain uncontrolled with the standard regimen<sup>13,28,29</sup>. In our study, nine patients (22%) had required higher doses of omalizumab. It is not elucidated why some patients needed shorter intervals of treatment while some not. Our earlier report<sup>13</sup> indicated that patients with a higher BMI and lower baseline UCT scores require higher doses to control the disease. However, we found in this study that the baseline UCT and IC-UAS scores as well as other parameters evaluated were unable to predict the need for higher doses.

The results of phase 3 clinical trials show that omalizumab is effective in controlling symptoms, but do not induce remission of CU<sup>4,5,24</sup>. On the other hand, cessation of omalizumab treatment causes return of CU symptoms in approximately in 4.7 weeks<sup>30</sup>. Although there is no consensus on how to cease omalizumab treatment, increasing the time interval between doses have been proposed by some authors rather than abruptly discontinuing the treatment<sup>14,19,31,32</sup>. Due to economical concerns, the dose intervals of patients, who achieved remission but still needed maintenance doses, were successfully extended to 6–8 weeks in Song et al.'s study<sup>14</sup>. Ensina et al.<sup>32</sup> reported one patient remained under control with 12 week intervals and did not have to take corticosteroids. In our centre, we usually start to treat with the recommended dose of omalizumab (300 mg/4 weeks) and if no urticaria activity is present (UAS7 = 0 last week before injection) after 3 monthly injections, we increase the dose intervals by 1-week in each visit (if UAS7 = 0 during last week) and cease the treatment when patients tolerate 12-week intervals. In case of disease exacerbations throughout the treatment, the dose intervals may eventually require to be re-adjusted. This is not due to loss of drug efficacy but rather due to the natural course of the disease<sup>33</sup>. In this case, the intervals may be reduced to the point that the patients can tolerate. Our study showed that the majority of the patients (92.7%) tolerated increasing dose intervals after a mean of 12 weeks of omalizumab treatment. While the median time of dose interval was 7 weeks in these patients, the longest dose interval was 14 weeks in one patient, which is the longest of known in the literature; we observed that no loss of

efficacy occurred in these patients. The XTEND-CIU study<sup>10</sup> indicated that most patients experienced a relapse when they discontinue omalizumab. In three studies, relapse rates have been reported in 100%, 87% and 47.5% of patients<sup>7,20,30</sup>. Considering these findings, we suggest trying to increase dose intervals in asymptomatic patients rather than abruptly ceasing omalizumab, since the aim of urticaria treatment is achieving symptom control and in the meantime we do not have the cure for the disease.

In the studies which relapse rates mentioned above, successfully retreatment with omalizumab have been reported in 100%, 100% and 90% of patients, respectively<sup>7,20,30</sup>. In our study, 80% of the patients who discontinued omalizumab needed retreatment due to relapse. All the retreated patients achieved symptom control, as the aforementioned studies.

Omalizumab is usually well-tolerated by the patients. The most common side effects reported in the trials and real life studies are mild to moderate including nasopharyngitis, upper respiratory tract infection, headache, dizziness, fatigue and injection site reactions<sup>3–6,34</sup>. In a systematic review of real world evidence of omalizumab<sup>34</sup>, it is reported that 6.6% of all included 1327 patients experienced an adverse event which was mild and transient and only 3 patients (0.2%) experienced anaphylaxis which remained unclear in 2 of them if it is omalizumab-related or not. This safety profile of omalizumab have been supported by other real life studies where omalizumab have been used more than 1 year<sup>19,32,33</sup>. Ensina et al.<sup>32</sup> and Silva et al.<sup>19</sup> observed no adverse reactions during omalizumab treatment. Pinto et al.<sup>33</sup> reported one patient with angioedema and urticaria aggravation and one patient with headache after receiving omalizumab 300 mg. In our study, five patients reported mild adverse effect presumably caused by omalizumab, including injection-site reactions, hair loss, malaise, menstrual irregularity and motion disability on hand joints. None of these symptoms recurred after following doses or caused discontinuation of omalizumab. Although omalizumab associated anaphylaxis was reported in two cases in XTEND-CIU study<sup>10</sup>, we did not observe any in a total of 1220 injections. The real-life report of Vollono et al.<sup>35</sup> indicated that omalizumab is also safe in CU patients with several comorbidities; likewise our patient cohort also had different comorbidities including myocardial infarction which did not seem to effect omalizumab's safety profile. Besides, no omalizumab related adverse event was noted by Metz et al.<sup>20</sup> in retreated patients. We also reported earlier that there is no significant adverse effect in patients receiving 600 mg omalizumab<sup>13</sup>. Moreover, we did not observe a significant change in patients' laboratory results including haematological parameters, liver and kidney functions after 3 years' of treatment. All these findings indicate that omalizumab may be used in long term without increased risk of adverse events.

The main limitations of this study were its retrospective and single-centre nature with limited number of patients.

## Conclusion

Omalizumab is an effective and safe treatment option for CU and our study shows this does not change in the long-term.

CU remission may occur spontaneously within several years of disease onset. Until that time, to provide symptom control in CU patients, individualized omalizumab dosing intervals might be beneficial for long-term management of CU as it is cost-effective and decreases hospital admissions.

## Disclosure statement

Dr Emek Kocaturk reports advisory board fees from Novartis, and has served as a medical advisor for Bayer and Sanofi. The other author has no conflict of interest to declare.

## References

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;73:1393–1414.
2. Mlynec A, Magerl M, Hanna M, et al. The German version of the Chronic Urticaria Quality-of-Life Questionnaire: factor analysis, validation, and initial clinical findings. *Allergy* 2009;64:927–936.
3. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015;135:67–75.
4. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924–935.
5. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013;132:101–109.
6. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2016;137:1742–1750 e4.
7. Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther* 2013;13:1225–1228.
8. MacDonald KM, Kavati A, Ortiz B, et al. Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008–2018. *Expert Rev Clin Immunol* 2019;15:553–569.
9. Mansur AH, Srivastava S, Mitchell V, et al. Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: study of efficacy and safety. *Respir Med* 2017;124:36–43.
10. Maurer M, Kaplan A, Rosen K, et al. The XTEND-CIU study: long-term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2018;141:1138–1139 e7.
11. Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004;59:869–873.
12. Turk M, Kocaturk E, Cure K, Yilmaz I. Two-week intervals during omalizumab treatment may provide better symptom control in selected patients with chronic urticaria. *J Allergy Clin Immunol Pract* 2018;6:1389–1390.
13. Kocaturk E, Deza G, Kiziltac K, Gimenez-Arnau AM. Omalizumab up dosing for better disease control in chronic spontaneous urticaria patients. *Int Arch Allergy Immunol* 2018;177:360–364.
14. Song CH, Stern S, Giruparajah M, et al. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. *Ann Allergy Asthma Immunol* 2013;110:113–117.
15. Maurer M, Metz M, Bindslev-Jensen C, et al. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. *Allergy* 2016;71:1210–1218.
16. Maurer M, Mathias SD, Crosby RD, et al. Validity and responsiveness of the Urticaria Activity and Impact Measure: a new patient-reported tool. *Ann Allergy Asthma Immunol* 2018;120:641–647.

17. Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014; 133:1365–72. 72 e1–6.
18. Kocaturk E, Kiziltac U, Can P, et al. Validation of the Turkish version of the Urticaria Control Test: correlation with other tools and comparison between spontaneous and inducible chronic urticaria. *World Allergy Organ J* 2019;12:100009.
19. Silva PM, Costa AC, Mendes A, Barbosa MP. Long-term efficacy of omalizumab in seven patients with treatment-resistant chronic spontaneous urticaria. *Allergol Immunopathol (Madr)* 2015;43: 168–173.
20. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol* 2014;150:288–290.
21. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci* 2014;73: 57–62.
22. Mandel VD, Guanti MB, Liberati S, et al. Omalizumab in chronic spontaneous urticaria refractory to conventional therapy: an Italian retrospective clinical analysis with suggestions for long-term maintenance strategies. *Dermatol Ther (Heidelb)* 2018;8:291–301.
23. Buyukozturk S, Gelincik A, Demirturk M, et al. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: a real life survey. *J Dermatol* 2012;39:439–442.
24. Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol* 2016;137:474–481.
25. Gericke J, Metz M, Ohanyan T, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;139:1059–1061 e1.
26. Nettis E, Cegolon L, Di Leo E, et al. Omalizumab in chronic spontaneous urticaria: efficacy, safety, predictors of treatment outcome, and time to response. *Ann Allergy Asthma Immunol* 2018;121: 474–478.
27. Turk M, Yilmaz I, Nazik Bahcecioglu S, et al. Effectiveness of as-needed antihistamines in chronic spontaneous urticaria patients under omalizumab treatment. *Dermatol Ther* 2021;34(1):e14543.
28. Clark JJ, Secrest AM, Hull CM, et al. The effect of omalizumab dosing and frequency in chronic idiopathic urticaria: retrospective chart review. *J Am Acad Dermatol* 2016;74:1274–1276.
29. Lefevre AC, Deleuran M, Vestergaard C. A long term case series study of the effect of omalizumab on chronic spontaneous urticaria. *Ann Dermatol* 2013;25:242–245.
30. Sussman G, Hebert J, Gulliver W, et al. Omalizumab retreatment and step-up in patients with chronic spontaneous urticaria: OPTIMA trial. *J Allergy Clin Immunol Pract* 2020;8(7):2372–2378.e5.
31. Kavati A, Zhdanova M, Ortiz B, et al. Long-term omalizumab outcomes in chronic idiopathic urticaria: a real-world study. *Allergy Asthma Proc* 2019;40:321–328.
32. Ensina LF, de Lacerda AE, Machado LM, et al. Long-term omalizumab therapy for refractory chronic spontaneous urticaria: a real-life experience. *Ann Allergy Asthma Immunol* 2015;115:536.
33. Pinto Gouveia M, Gameiro A, Pinho A, Goncalo M. Long-term management of chronic spontaneous urticaria with omalizumab. *Clin Exp Dermatol* 2017;42:735–742.
34. Bernstein JA, Kavati A, Tharp MD, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. *Expert Opin Biol Ther* 2018;18:425–448.
35. Vollono L, Piccolo A, Lanna C, et al. Omalizumab for chronic spontaneous urticaria in "complex" patients: data from real-life clinical practice. *Drug Des Devel Ther* 2019;13:3181–3186.