



# Omalizumab in chronic urticaria: A comprehensive review

## *Kronik ürtikerde omalizumab: Kapsamlı bir derleme*

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### Abstract

Omalizumab is a humanized monoclonal anti-immunoglobulin E which is originally developed for the treatment of allergic respiratory disorders, but has been approved for the treatment of antihistamine-resistant chronic spontaneous urticaria in 2014. It has become a game changer in the treatment of all subtypes of chronic urticaria (CU) even though it has not been yet approved for inducible urticarias. It is a safe drug with minor adverse events reported in the clinical trials as well as real life studies. The main questions that remain to be answered regarding its use for CU are the duration of treatment, how to cease the treatment and safety of long-term use. Available information about these questions are tried to be provided in this review.

**Keywords:** Omalizumab, chronic urticaria, physical urticaria, treatment

### Öz

Humanize monoklonal anti-immunoglobulin E antikoru olan omalizumab ilk kez alerjik solunum yolu hastalıklarının tedavisi için geliştirilmiş olup 2014 yılında antihistamin dirençli kronik spontan ürtiker tedavisi için onay almıştır. Henüz indüklenbilir ürtikerin tedavisinde onaylanmamış olmasına rağmen tüm kronik ürtiker (KÜ) alt tiplerinde başarılı bir şekilde uygulanmaktadır. Klinik çalışmalarda ve gerçek yaşam verilerinde bildirilen hafif yan etkiler güvenli bir ilaç olduğunu düşündürmektedir. KÜ'deki kullanımına ait cevaplanmamış sorular kullanım süresi, tedavinin nasıl kesileceği ve uzun dönem yan etkileridir. Bu derlemede bu sorulara ilişkin cevaplar verilmeye çalışılmaktadır.

**Anahtar Kelimeler:** Omalizumab, kronik ürtiker, fiziksel ürtiker, tedavi

### Introduction

Omalizumab is a humanized recombinant monoclonal anti-immunoglobulin E (IgE) which was originally developed for the treatment of allergic respiratory disorders<sup>1</sup>. It was first approved for the treatment of moderate-severe persistent asthma in the US in 2003<sup>2</sup> and for severe allergic asthma in the EU in 2005<sup>3</sup>. Subsequent to evidence suggesting its efficacy on chronic urticaria (CU), phase studies were performed and omalizumab was approved for the treatment of antihistamine-resistant chronic spontaneous urticaria (CSU) in 2014<sup>2,3</sup>.

Omalizumab acts by preventing the binding of IgE to the high-affinity receptors (FcεRI) on mast cells and basophils<sup>4</sup>. Its efficacy has been demonstrated in antihistamine-resistant CSU patients by case reports, case series, observational studies, and randomized placebo-controlled studies<sup>5-11</sup>. It is the only approved add-on treatment for CSU patients aged 12 years or older who do not respond to H1 antihistamines in both Europe and the US<sup>12</sup>. The efficacy of omalizumab has not only been demonstrated in autoimmune urticaria, but also in the physical, cholinergic, and other forms of urticaria<sup>13</sup>. It has been approved for the treatment of antihistamine-resistant CSU/chronic idiopathic urticaria (CIU)

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in Turkey by September 2013 and it is reimbursed in CSU patients with at least 6 months of disease duration when the predefined procedural prerequisites are met<sup>14</sup>.

Omalizumab appears to be a safe and well-tolerated drug. The most common side effects observed with omalizumab are the injection site reactions (40%) (pain, swelling, erythema, and itching) and urticaria (4.9%)<sup>15</sup>. Anaphylaxis has been reported in 0.09% of patients with allergic asthma. It is recommended that the drug should be administered in sufficiently well-equipped clinical conditions<sup>16</sup>.

## Mechanisms of action

Although it is clear that omalizumab is an effective treatment for many patients with CIU/CSU, the mechanism of action still remains uncertain. One of the most likely mechanisms of action of omalizumab in CSU is to stabilize mast cells by preventing the degranulating effect of monomeric IgE on these cells. In cases with autoimmune urticaria, sequestration of IgE by omalizumab causes a decrease in mast cell-IgE bounds, followed by downregulation of FcεRI receptors on mast cells and basophils which increase threshold levels of excitability of these cells. Stabilization of basophils cause a decrease in inflammatory cytokines and mediator release, and skin inflammatory processes diminish as a consequence. This overall effect is important, especially in the first phase of the treatment period, owing to downregulation of FcεRI on basophils being faster than that of mast cells<sup>17</sup>. A summary of potential mechanisms of action of omalizumab are shown in Table 1<sup>18,19</sup>.

## Pharmacokinetics of omalizumab

Omalizumab is an IgG1 kappa monoclonal antibody of recombinant DNA origin that binds to the human IgE selectively. It has a molecular weight of 149 kDa and 95% of its structure is of human origin and the remaining 5% originates from rodents (mouse and rabbit)<sup>20,21</sup>.

Following the subcutaneous administration of omalizumab, it is absorbed with an average absolute bioavailability rate of 62%. After the administration of a single dose, omalizumab achieves maximum serum concentrations in 7-8 days. Stable serum levels are reached in up to 14-28 days following repeated administrations<sup>14,21,22</sup>.

A larger portion of omalizumab is degraded by the reticuloendothelial system of the liver, whereas, a smaller intact portion is excreted through

the bile. Omalizumab-IgE complex is more rapidly eliminated than free omalizumab, however, it is eliminated more slowly than free IgE. The half-life of the drug is similar to that of human IgG, ranging from 3 to 4 weeks (with a mean of 26 days). The pharmacokinetic effects of the drug do not depend on age, gender, race or the diseases for which it is administered<sup>14,23</sup>.

Yielding these inherent features, omalizumab was primarily developed for the treatment of allergic respiratory infections, of which the main impact of IgE has been well-recognized on the pathogenesis. During the initial years of its use, patients with moderate to severe persistent chronic asthma were treated with omalizumab. This was followed by use in allergic asthma. Eventually, in the light of the study data, it has been used in the treatment of patients with CU unresponsive to the conventional treatments<sup>24</sup>.

## Omalizumab phase studies for chronic spontaneous urticaria

A multi-center, randomized, double-blind, placebo-controlled study (X-QUISITE) by Maurer et al.<sup>25</sup> evaluating the efficacy and safety of omalizumab in CSU patients positive for IgE antibodies against thyroid peroxidase, determined the treatment doses (75 mg-375 mg) using a dosing schedule for asthma. Out of 49 randomized patients (omalizumab n=27, placebo n=22), 42 completed the study. Compared with placebo, they found a significant decrease in the Urticaria Activity Score summed over 7 days (UAS7) in the 24<sup>th</sup> week in both groups. These results have suggested that, unlike the treatment of asthma, it is not required to adjust the doses depending on the patients and fixed doses might be beneficial.

Consequently, single fixed doses of 75 mg, 300 mg, 600 mg omalizumab or placebo were used for the treatment of patients in a phase 2 study (MYSTIQUE) to determine the most effective dose with 90 patients. It was determined that the treatment efficacy achieves its peak at 300 mg, then reaches a plateau. The treatment doses of 300 mg and 600 mg were found to be more efficacious than placebo, however, no significant differences were observed with 75 mg compared to placebo. The average reductions in the UAS7 were 13 and 7.7 in the omalizumab 300 mg and 600 mg groups in the fourth week, respectively. The results obtained in the 75 mg omalizumab group were same as in the placebo group. This study has proposed that a treatment dose of 300 mg omalizumab can be the optimal dose in the treatment of urticaria symptoms (MYSTIQUE)<sup>24,26</sup>.

The study by Maurer et al.<sup>25</sup> found a 70% rate of achieving UAS7=0 in the 24<sup>th</sup> week, whereas, the study by Saini et al.<sup>26</sup> demonstrated that 36% of the patients achieved UAS7=0 in the 4<sup>th</sup> week.

The multi-center, randomized, double-blind, phase 3 study (ASTERIA 2) with 323 patients by Maurer et al.<sup>11</sup> demonstrated that omalizumab, in 150 mg and 300 mg doses, was significantly more efficacious than placebo, whereas the treatment dose of 75 mg was inefficacious in diminishing the symptoms. The secondary end-points of this study reported that in the placebo, 75 mg, 150 mg, and 300 mg groups; the proportions of the patients achieving UAS7=0 in the 12<sup>th</sup> week were 5%, 16%, 22%, and 44%, respectively, while the proportion of the patients with UAS7≤6 were 19%, 27%, 43%, and 66%, respectively.

**Table 1. The mechanisms of action of omalizumab in chronic spontaneous urticaria**

1. Decreases IgE serum levels and downregulates IgE receptors
2. Reduces mast cell discharge potential
3. Increases number of basophils and improves basophil IgE receptor function
4. Diminishes activity of IgG autoantibodies against IgE and FcεRI
5. Reduces activity of innately "abnormal" IgE
6. Downregulates affinity of IgE autoantibodies against an autoantigen
7. Prevents release of inflammatory mediators via decrease in number of IgE bindings
8. Decreases the impact of coagulation system on disease
Ig: Immunoglobulin, FcεRI: Immunoglobulin E to the high-affinity receptors

Another multicenter, randomized, double-blind, placebo-controlled study (ASTERIA I) to evaluate the efficacy and safety of subcutaneous omalizumab was conducted by Saini et al.<sup>27</sup> with 319 patients for 40 weeks. The patients were randomized in a double-blind manner to subcutaneous omalizumab 75 mg, 150 mg, or 300 mg or placebo every 4 weeks for 24 weeks with a subsequent 16 weeks of follow-up. This study reported that the proportions of the patients achieving UAS7  $\leq 6$  and UAS7=0 in the omalizumab 300 mg group in the 12<sup>th</sup> week were 51.9% and 35.8%, respectively. In the 24<sup>th</sup> week, they were 62% and 48% for the UAS7  $\leq 6$  and UAS7=0, respectively<sup>28</sup>. Overall, this study showed a sustained treatment effect of omalizumab 300 mg for up to 24 weeks on CIU/CSU<sup>27</sup>.

Kaplan et al.<sup>10</sup> conducted the phase 3 study (GLACIAL) to assess the safety and efficacy of 24 weeks of treatment with omalizumab in patients with CIU/CSU which was persistent despite treatment with H1-antihistamines at up to four-fold the approved dose plus H2-antihistamines, leukotriene receptor antagonists, or both. 335 patients were randomized to receive 6 subcutaneous injections at 4-week intervals of either 300 mg of omalizumab or placebo, followed by a 16-week observation period. Significant improvements were seen in week 12; these benefits were continued to week 24.

The studies conducted by Saini et al.<sup>27</sup> and Kaplan et al.<sup>10</sup> reported the proportion of the patients achieving a score of UAS7  $\leq 6$  in the 24<sup>th</sup> week but not in the 12<sup>th</sup> week as 58.1% and 38.2%, respectively<sup>28</sup>.

## Omalizumab's real-life experiences in chronic spontaneous urticaria

Labrador-Horrillo et al.<sup>29</sup> administered treatment with 150 or 300 mg doses of omalizumab every 2 or 4 weeks to their patients regardless of their body weights and total IgE levels. In a retrospective study by Rottem et al.<sup>30</sup>, omalizumab was administered at 150 mg and 300 mg doses for a duration of 4 weeks to groups of 30 and 13 patients, respectively. On the other hand, Sussman et al.<sup>31</sup> administered 150 mg omalizumab for a duration of 4 weeks to all patients.

Ghazanfar et al.<sup>32</sup> discussed the efficacy of the omalizumab treatment in a retrospective study which included 154 CU patients. 89% of the study patients were diagnosed with CSU. Hundred and ten (71.4%) patients were female and 44 (28.6%) were male. 45.5% and 55% of patients were administered 150 mg/2-week and 300 mg/4-week treatments, respectively. Omalizumab was administered at 150 mg/2-week and 300 mg/4-week doses to 62 (54.3%) and 75 (54.7%) CSU patients, respectively. Consequently, no significant differences in the treatment responses were observed between the two treatment groups receiving omalizumab 300 mg/4 weeks and 150 mg/2 weeks. The real life studies report an 80% response rate to omalizumab<sup>29,33</sup>. However, in terms of evaluating the treatment response, it is not possible to compare the study results to each other due to the fact that standard methodologies were not employed<sup>12</sup>.

Twelve antihistamine-resistant CSU patients were administered omalizumab treatment in a study conducted in Turkey by Büyükoztürk et al.<sup>9</sup> Following the initial dose, all patients achieved the treatment response at the end of the first week. All the 12 patients enrolled in the study showed significant decreases in their UASs and CU quality of life (QoL) scores at the end of the first month. These responses

were maintained for six months. Differences observed in the CU-QoL survey scores were observed in all sub-scales with statistical significance compared to the baseline.

Another prospective study was conducted at two clinical sites in Toronto and Quebec. The study was planned to investigate the efficacy of 150 mg/4-week treatment in patients with CU resistant to conventional treatments. Sixty-eight patients were included in the study. Of them, 61 had a diagnosis of CSU, 6 had cold urticaria (ColdU), and 1 of them had been diagnosed with urticarial vasculitis. The patients had been followed up for 25 months. A 69% complete remission UAS7=0 rate was achieved in the whole patient population<sup>31</sup>.

Giménez-Arnau et al.<sup>34</sup> administered 300 mg/4-week omalizumab treatment to 38 patients in their study and observed a significant decline in UAS7. Following the treatment administration, 68.6% of the patients achieved the response with the UAS7=0 and 23.7% achieved the response with UAS7  $\leq 6$ .

In a retrospective analysis including 110 CSU patients treated with omalizumab at 9 separate centers, no differences were observed in the treatment response and the required time to elapse for the emergent treatment response when the CSU patients were compared to CSU patients with accompanying physical urticaria, angioedema, and autoimmunity<sup>29</sup>.

A retrospective study conducted by Metz et al.<sup>33</sup> reported that of the 30 CSU patients in the study [20 of them were diagnosed only with CIU, whereas, 10 were diagnosed with both CIU and chronic inducible urticaria (CIndU)]; 25 (83%) patients achieved a complete remission and 3 (10%) showed significant improvements, however, only 2 (7%) patients were non-responsive.

Another retrospective multicenter study from Israel with 43 patients supported that omalizumab was an effective and safe treatment for refractory CSU. In this study, 13 patients received 300 mg omalizumab/month while 30 patients received 150 mg once or more. The overall rate of response to omalizumab in this study was 86%, with 57% of responders showing complete response and 43% a partial remission<sup>30</sup>. Vadasz et al.<sup>35</sup> retrospectively analyzed 280 patients in whom omalizumab was started (50 patients 150 mg/month, 230 patients 300 mg/month). Overall, well-controlled response was recorded in 63% of treated patients; in 25%, there was a fair-weak response, and in 12% therapy failed.

## Efficacy in chronic inducible urticarias

The study conducted by Sussman et al.<sup>31</sup>, treating 6 ColdU patients with omalizumab, reported that all patient symptoms were resolved as observed in the cold stimulation test.

Metz et al.<sup>33</sup> studied omalizumab in 34 patients with several forms of CIndU and reported a 71% treatment response rate. On the other hand, they determined that majority of the CIndU patients needed dose increases compared to the CSU patients in order to achieve a complete response. Ghazanfar et al.<sup>32</sup> reported a response rate of 53% with omalizumab treatment in 17 patients with CIndU.

Kocatürk Göncü et al.<sup>36</sup> treated 17 CIndU patients [10 patients with symptomatic dermatographism (SD), 2 with cholinergic urticaria, 2 with ColdU, with combined CIndU and 1 with aquagenic urticaria (AU) with omalizumab (150 mg every 2 weeks or 300 mg every 4 weeks)]. Ten (58.8%) patients with CIndU achieved good symptom control at week

4 while 13 (76.5%) patients at week 8, and 11 patients (64.7%) at week 12 responded to treatment. Fourteen out of 17 CIndU patients had continued follow-up until 24<sup>th</sup> week of omalizumab treatment. Eleven (78.6%) patients in the CIndU group responded to omalizumab treatment at the 24<sup>th</sup> week.

Maurer et al.<sup>37</sup> reviewed a total of 43 studies, including case studies, case reports, and retrospective analyses on CIndU patients treated with omalizumab. The review reported that there were phase 2 studies in solar urticaria<sup>38</sup>, ColdU<sup>39</sup>, and SD<sup>40</sup>. It was reported that the phase 2 studies on ColdU and SD were randomized and placebo-controlled<sup>39,40</sup>. The majority of the published evidence in the literature included single case reports, case studies conducted with a small number of patients or studies which enrolled CSU patients as well. In conclusion, it was demonstrated that omalizumab provided significant benefits in several forms of CIndU. In the light of information provided by the conducted studies, the highest level of evidence was provided by the studies conducted in patients with SD, ColdU and solar urticaria. The number of studies on vibratory angioedema, AU, and contact urticaria is quite limited and therefore, the level of evidence was reported to be lower. The randomized study by Maurer et al.<sup>40</sup> observed statistically and clinically meaningful reductions in the disease activity, as well as in the impact of the disease on QoL, in the SD patients treated with omalizumab 150 mg or 300 mg. Consequently, both 150 mg and 300 mg doses of omalizumab were found to be effective and no statistically significant differences were observed between these two doses. On the other hand, in patients with CSU, efficacy was observed with these two doses of omalizumab, however, the efficacy of the 300 mg doses was determined to be higher.

The randomized study conducted in ColdU patients by Metz et al.<sup>39</sup> reported that omalizumab, in 150 mg and 300 mg doses, helped higher proportions of patients with complete and partial responses, decreasing the disease activity significantly. Interestingly, 150 mg and 300 mg doses were found to be similarly effective. The results show that ColdU patients, who are non-responsive to antihistamines, may be treated with omalizumab, a well-tolerated and effective treatment.

## Indicators of the treatment response

There has been a continuous effort to find a biomarker or indicator which would predict response to omalizumab, since this would be very beneficial for aiding decisions in clinical practice. For this purpose, Asero et al.<sup>41</sup> investigated the change in the plasma levels of D-dimer in CSU patients receiving omalizumab treatment. They found that D-dimer levels had a parallel course with the treatment response to omalizumab, decreasing in individuals with the treatment response and remaining unchanged in non-responsive individuals. They concluded that D-dimer was a positive predictive indicator for the clinical response during anti-IgE treatment. The authors also observed that gender, age, and disease duration did not affect the clinical response to omalizumab.

Pinto Gouveia et al.<sup>42</sup> reported that there was no statistically significant correlation between the treatment responses with respect to gender, age, disease severity, C-reactive protein (CRP), IgE levels, previous therapies, histopathological findings and serological evidence of autoimmunity.

Vadasz et al.<sup>35</sup> reported that patients with a poor response to omalizumab treatment had longer disease duration and higher UAS7 compared to patients experiencing better treatment responses.

Ertas et al.<sup>43</sup> reported accompanying more frequent angioedema and a higher disease activity in the patient group without response. The baseline levels of total IgE were found to be lower in patients who do not respond to omalizumab treatment. Comparison of the mean baseline IgE levels revealed IgE levels of 17.9 IU/mL, 82.0 IU/mL, and 73.7 IU/mL in non-responsive patients, in patients with partial response and in patients who achieved complete response, respectively. This finding was also confirmed by a recent observation by Straesser et al.<sup>44</sup> Clayton and Saltoun<sup>45</sup> reported an overall combined partial and complete response rate of 86.5% to omalizumab treatment. A significant difference in the number of regularly used medicine previously was observed in each group. The response rates of patients with accompanying eczema were found to be lower. Patients with neutrophilic urticaria tended to demonstrate lower response rates. The treatment response was not found to be correlated with angioedema, anaphylaxis, dermatographism or steroid use. The response rates were also not correlated with the disease duration.

Ghazanfar et al.<sup>32</sup> found that CSU was associated with a higher percentage of complete or almost complete responders compared with CIndU, as assessed by Physician's Global Assessment grading (67.4% vs. 52.9%, respectively). Moreover, there was a tendency for improved treatment response with older age at onset and shorter disease duration. Additionally, among the patients with CSU, a greater percentage of complete/almost complete responders had a negative histamine release test, did not have angioedema and had no prior history of treatment with systemic immunosuppressants.

Palacios et al.<sup>46</sup> found that a lack of basophil CD203c-upregulating activity in the serum of patients with CU has been found to correlate with clinical response to omalizumab.

Gericke et al.<sup>47</sup> suggested that basophil histamine release induced by CSU sera seems to correlate with a slow response to omalizumab, and may represent a future biomarker. In a recent review, Basophil Histamine Release Assay, autologous serum skin test, and basophil CD203c-upregulating activity in the serum were also mentioned as potential biomarkers for determining response to omalizumab<sup>48</sup>.

A study by Deza et al.<sup>49</sup> demonstrated that CSU patients showing significant clinical improvement exhibited a sharp reduction in the levels of basophil FcεRI after 4 weeks of omalizumab treatment, which was continued during the treatment. Such evolution was not observed in non-responder patients. Non-responder patients had significantly lower baseline levels of FcεRI than responders. Baseline basophil FcεRI expression was found to be a potential immunological predictor of response to omalizumab.

## Administration, treatment intervals and ceasing treatment

Omalizumab is recommended for the treatment of CSU at doses of 150-300 mg/every 4 weeks in the US<sup>2</sup> and 300 mg in the EU regardless of serum IgE levels<sup>3</sup>.

However, an individualized approach might be beneficial for some patients. For instance, some patients might not tolerate 4 weeks dosing intervals and experience return of symptoms before week 4. In this subset of patients, implementation of 150 mg of omalizumab at 2-week intervals might provide symptom control<sup>50</sup>.

There is no consensus on the duration of treatment, though many physicians would cease treatment at 6 months and wait for the relapse of the disease.

Relapse rates have been reported to be 100%, 47.5%, 61%; and retreatment with omalizumab has been reported to be successful in 100%, 90% and 56% of patients, respectively<sup>13,29,51</sup>. In the OPTIMA study, after treatment withdrawal, 44% of patients on 150 mg and 50% on 300 mg relapsed (UAS7  $\geq$ 16) within 8 weeks. Upon retreatment, the majority of patients achieved UAS7  $\leq$ 6 in the 2<sup>nd</sup> dosing period (150 mg: 83.3%; 300 mg: 89.2%)<sup>52</sup>.

Approaches to tapering, such as decreasing the dose or prolonging dosing intervals, or discontinuation of omalizumab treatment have been proposed by some authors.

Uysal et al.<sup>53</sup> performed a small single-arm open-label study which included 27 patients with CU who were started on 150 mg of omalizumab. After 2 weeks, physicians evaluated each patient's condition and prescribed the next dose based on how the patient responded. Approximately 56% (15/27) of patients reached a UAS $>$ 2 after a single 150 mg omalizumab dose and stayed in this dose category, and the remaining patients (12/27) received 300 mg of omalizumab at week 3 and remained in this dose category. According to the authors, this approach was cost-effective and decreased hospital admissions. Vadasz et al.<sup>35</sup> found that increasing the dose intervals to 6-8 weeks was possible in only a few patients.

There is no consensus for partial responders or non-responders receiving 300 mg/every 4 weekly administrations, however, there are some recommendations from authors who are experienced in using this drug. For instance, Giménez-Arnau et al.<sup>54</sup>, Kocatürk Göncü et al.<sup>55</sup>, and Curto-Barredo et al.<sup>56</sup> recommend increasing the dose to 450 mg or 600 mg if no response is achieved after administering omalizumab 300 mg for 6 months. Vadasz et al.<sup>35</sup> also increased the dosage of omalizumab when the response was weak after 3 months. Cases are considered to be resistant in the absence of a response after a 3-month treatment with 600 mg omalizumab<sup>54</sup>. Har et al.<sup>57</sup> also reported that in patients with partial response, symptom control was improved with more frequent dosing of omalizumab (300 mg every 2-3 weeks).

Currently, there is not a consensus approach for ceasing omalizumab therapy. Several strategies have been proposed for ceasing, including reducing monthly doses or lengthening the time interval between doses.

As demonstrated in phase 3 trials, cessation of omalizumab treatment causes an increase in weekly symptoms and returning to placebo levels within 16 weeks<sup>10,11,28</sup>. These controlled trials show that omalizumab is effective in controlling symptoms, but do not claim that omalizumab induces remission of CIU. The authors of this review (Kocatürk Göncü et al.<sup>55</sup>) typically treat responders for approximately 6 months at monthly intervals and if no minimal urticaria activity is present, increase the injection interval by 1-week intervals (ie, every 5 weeks then 6 weeks etc) and cease the treatment when patient tolerates 12 weeks of intervals. Joshi and Khan<sup>58</sup> suggests that if a patient can tolerate every 8-week injections over a 4-month period without increased disease activity, these patients can often have omalizumab discontinued. Tontini et al.<sup>59</sup> proposed a patient-tailored tapering protocol to customize weaning regimens on the basis of a patient's UAS7 while on omalizumab.

If there is no response to omalizumab after six months of treatment, Metz et al.<sup>13</sup> advise deeming the patient to be a non-responder, discontinuing omalizumab and considering an alternative treatment

option. In treatment responders, omalizumab treatment can be resumed at a later stage after discontinuation with the same degree of symptom control.

Ferrer et al.<sup>60</sup> recommend stopping treatment and considering an alternative drug in patients if there is no response to omalizumab after six months. They also recommend an algorithm for when to restart treatment in patients who have previously taken omalizumab and left treatment after entering remission. According to their recommendations, if patients have a UAS7 $>$ 6 and/or urticaria control test score  $<$ 12 (indicating active disease and/or poor disease control) during follow-up, then continued treatment is advised. This is also dependent on physician judgement and the patient's own expectations. For example, depending on their previous disease activity, some patients may be content to live with moderate CSU and their physician may propose to restart treatment when their UAS7 is  $>$ 16. They also emphasize the importance of considering the presence or absence of angioedema during evaluating response and managing treatment. They also advise physicians to consider reducing the dose of omalizumab and/or increasing the dosing intervals, or discontinuing omalizumab to assess for spontaneous remission if a complete response has been present for 3-6 months.

Urticaria treatment aims at achieving total symptom control. With this in mind, we have come to the conclusion that most reasonable method for patients who have reached full remission should be to intermittently try increasing injection intervals or reduce the dose to 150 mg.

## Omalizumab and side effects

Omalizumab is usually well-tolerated by the patients. The side effects reported in CSU patients were in alignment with those reported in the placebo group and with those reported by the studies conducted with patients with allergic asthma<sup>10,11,26,28,61</sup>. The most common side effects included nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, headache, and cough<sup>61</sup>. ASTERIA 1, 2 and GLACIAL study results demonstrate that the proportion of the patients reporting at least 1 side effect in week 12 was higher in the omalizumab group (150 mg, 54.9%; 300 mg, 51.0%) compared to the placebo group (42.6%). Majority of the reported side effects were mild and moderate. Severe side effects were observed in the placebo group at a rate of 6.2%, whereas, they were observed in the omalizumab 300 mg treatment group less frequently, at a rate of 5.3%. Furthermore, the proportion of the patients leaving the study due to severe side effects was higher (5.4%) in the placebo group, compared to the omalizumab 300 mg group (3.6%) and omalizumab 150 mg group (3.4%)<sup>24,61</sup>.

The most common side effects reported in the real-life data included nausea, headache, dizziness, fatigue, and injection site reaction. No serious side effects were reported in these studies. Metz et al.<sup>33</sup> reported a patient who developed moderate angioedema. Rottem et al.<sup>30</sup> reported a patient who developed palpitation and lassitude in the 2<sup>nd</sup> hour following the administration of omalizumab. In the latter, no further complaints were experienced with further injections during the treatment course and omalizumab treatment continued. Recently, Konstantinou et al.<sup>62</sup> have reported 3 female patients with a mean age of 56.6. They experienced temporary alopecia, which has been suggested to be a potential side effect of omalizumab<sup>63</sup>.

Omalizumab associated anaphylaxis was reported in the XTEND-CIU study in two cases<sup>64</sup>. A triphasic anaphylaxis developed in a patient after an omalizumab injection<sup>65</sup>. In addition, Ertaş et al.<sup>66</sup> reported exacerbations of angioedema and/or urticaria in 4 patients following an omalizumab injection.

The Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) assessed the long-term safety of omalizumab in a clinical practice setting as part of a phase IV US Food and Drug Administration postmarketing commitment. Results from EXCELS suggest that omalizumab therapy is not associated with an increased risk of malignancy<sup>67</sup>.

## Long term efficacy

To date, one randomized controlled trial and few retrospective studies have examined the long-term efficacy of omalizumab beyond 24 weeks of treatment. One of the few prospective studies about long-term efficacy and safety of omalizumab is the US-based, phase IV, multicenter, randomized, double-blind, placebo-controlled XTEND-CIU study.

The XTEND-CIU study provides more information on the efficacy and safety of omalizumab over a longer term in patients with CIU/CSU. Continued omalizumab treatment was beneficial for patients both by preventing return of symptoms and by achieving sustained control through 48 weeks of treatment. The percentage of patients who experienced clinical deterioration for 12 weeks after leaving treatment was similar to that of those treated for 24 weeks before withdrawal and for 48 weeks before withdrawal. This demonstrated a need for treatment with omalizumab beyond 48 weeks. Maintained treatment with omalizumab prevents relapse and improves QoL. When it is needed, re-treatment can be done safely and effectively<sup>65</sup>.

One of the retrospective studies published by Har et al.<sup>57</sup> analysed 10 treatment refractory CU patients who received omalizumab treatment for longer than 1 year between 2005 and 2015. The study reported that 80% of patients showed complete response to treatment and all of them sustained a symptom-free status for longer than one year without increased dosage, increased dosage frequency or add-on therapy.

Another retrospective study included analysis of 110 treatment-refractory CSU patients treated in 9 Spanish hospitals between 2009 and 2012. The study presented data of omalizumab use in CSU over 3 years including >2000 doses, suggesting that omalizumab (150 and 300 mg once or twice per month) is effective for long-term use<sup>35</sup>. Of the 110 patients included in the analysis, 41 discontinued omalizumab treatment (after 1 to 18 months) because of good response; 21 remained free of symptoms, and 20 required re-treatment. The authors declared that omalizumab has an excellent profile in terms of efficacy/adverse events, with a response rate of 81% and a low percentage (7%) of patients with refractory CSU exhibiting a lack of response<sup>29</sup>.

Pinto Gouveia et al.<sup>42</sup> published a prospective study about long-term management of CSU with omalizumab. The authors reported that they did not identify any clinical or laboratory factors predicting response to omalizumab treatment in the study. Also age, sex, previous therapies, disease severity (baseline UAS7), CRP, pretreatment IgE level,

histopathological findings and serological evidence of autoimmunity were found to be independent of improvement of disease control. They noted that, despite providing effective symptom control or relief, omalizumab does not alter the natural course of the disease, which is characterized by spontaneous remission and exacerbation. In addition, fluctuations in response to omalizumab treatment seem not to be due to loss of drug efficacy but rather to natural exacerbations of the disease, which may occasionally require higher doses.

## Conclusion

Subsequent to all the knowledge and experience gained in its use, omalizumab has become a game changer in the treatment of CU. With a favourable safety profile and ease of use, it provides a very good treatment option which is the only approved treatment for antihistamine-resistant CSU. The dramatic response to treatment opened new horizons for the pathophysiology of CSU in which the role of IgE autoallergy has now gained attention. Questions that remained to be answered are the mechanism of action, biomarkers for treatment response, duration of treatment, how to cease the treatment, and long term safety.

## Ethics

**Peer-review:** Internally peer-reviewed.

## Authorship Contributions

Concept: E.K.G., K.K., T.L., Design: E.K.G., K.K., T.L., Data Collection or Processing: K.K., E.K.G., Analysis or Interpretation: E.K.G., T.L., Literature Search: K.K., E.K.G., Writing: K.K., E.K.G.

**Conflict of Interest:** Emek Kocatürk Göncü has offered consultancy Novartis. Tabi Leslie and Kübra Kızıldağ have not reported any conflict of interest.

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