



## The potential role of omalizumab in the treatment of chronic urticaria

Treatment of chronic urticaria refractory to antihistamines presents a challenge to both people affected with the disease as well as the physicians who treat them. Omalizumab, a monoclonal antibody against IgE, has emerged as one potential solution to this challenge. In several clinical trials published between 2011 and 2013, omalizumab significantly reduced or eliminated symptoms of chronic urticaria. The optimal dose for chronic urticaria is 300 mg administered every 4 weeks, a dose that differs from those used in asthma, which are based on the patient's weight and IgE level. Omalizumab does not appear to cause lasting symptom remission, and the ideal duration of treatment for chronic urticaria has not been defined.

**Keywords:** anti-IgE • chronic urticaria • clinical trial • hives • omalizumab

### Introduction to chronic urticaria

Chronic urticaria is defined as hives on most days of the week for more than 6 weeks [1]. Approximately 20% of cases are due to physical stimuli, and of the remainder, the majority are considered to be idiopathic [2]. In half of the cases, there is evidence for an autoimmune process, based on a positive autologous serum skin test, basophil histamine release or basophil activation testing, but the evidence that chronic urticaria is an 'autoimmune' disease is controversial [3]. Approximately 3% of the population suffers from chronic urticaria at some point in their lives [4]. The EAACI/GA<sup>2</sup>LEN/EDF/WAO Urticaria Treatment Guidelines recommend initial treatment with standard doses of nonsedating antihistamines, and increased doses up to four-times the standard in those who do not respond to standard doses [5]. Depending on the population studied and dose of antihistamines used, approximately 10–50% of cases of chronic urticaria will not respond to antihistamines [6,7]. For those patients, the guidelines recommend addition of leukotriene receptor antagonist or changing the nonsedating antihistamine, and use of steroids for flares for 3–7 days at a time [5].

However, the toxicity of corticosteroids makes them undesirable for long-term treatment [8]. If patients are still symptomatic, immunomodulatory treatment with cyclosporine or dapsone is recommended in the EAACI guidelines. Omalizumab (Xolair®, Genentech Inc., CA, USA) is also mentioned as an option for treatment. A position paper from the World Allergy Organization published in 2012 makes similar recommendations [9]. A recent review article proposes 'step-up/step-down' treatment for those who have failed other treatments, specifically, cyclosporine and omalizumab comprise the fourth step in the treatment approach [10]. In March 2014, omalizumab was approved in Europe and in the USA as add-on therapy for the treatment of chronic spontaneous urticaria in adults and adolescents with inadequate response to H1-antihistamine treatment [11].

Immunomodulatory treatment with cyclosporine has the greatest quantity of published data, and the evidence was outlined in a recent review article [12]. Another immunomodulatory treatment with success in urticaria is mycophenolate mofetil [13,14]. There is also evidence for efficacy of other anti-inflammatory and

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immunomodulatory treatments including sulfasalazine, hydroxychloroquine and methotrexate in treatment of chronic urticaria [15,16]. However, each of these medications have significant limitations, including slow onset of action of weeks to months with sulfasalazine, hydroxychloroquine and dapsone, and potentially serious side effects that require intensive monitoring including hypertension and renal failure with cyclosporine, and teratogenicity with mycophenolate mofetil [12,17]. Thus, omalizumab is an attractive treatment option, given its relatively benign side-effect profile and generally rapid onset of action.

### Introduction to omalizumab

Omalizumab is a recombinant humanized monoclonal antibody to IgE. It was created by inserting a mouse complementarity-determining region of monoclonal anti-IgE onto the consensus sequence of human IgG1. Omalizumab binds to IgE at the CH3 domain, which is the same epitope that binds to the  $\alpha$ -chain of Fc $\epsilon$ RI, the high-affinity IgE receptor. Thus, omalizumab forms complexes with circulating, non-receptor-bound IgE and once IgE is bound to omalizumab, it cannot bind to its receptor [18]. For this reason, omalizumab does not induce spontaneous histamine release from surface-bound IgE on basophils and mast cells. Complexes of IgE and omalizumab are primarily heterotrimers. By binding up free IgE, omalizumab decreases the availability of IgE to bind to IgE receptors. IgE bound to Fc $\epsilon$ RI stabilizes the Fc $\epsilon$ RI on mast cells and basophils. A loss of free IgE able to bind to Fc $\epsilon$ RI thus results in decreased expression of high-affinity IgE receptors on mast cells and basophils [19]. After 3 months of treatment with anti-IgE antibody in 15 atopic patients, free IgE decreased to 1% of prior levels and Fc $\epsilon$ RI levels decreased from 220,000 to 8300 receptors per basophil, which is approximately 4% of pretreatment levels. In a subset of these patients, this decrease in number occurred over only 3 days [20]. A similar effect on skin mast cells was demonstrated in three patients with allergic rhinitis undergoing intradermal skin testing and subsequent skin biopsy. Compared with controls, those treated with omalizumab had decreased skin mast cell expression of Fc $\epsilon$ RI, as measured by the expression of the  $\alpha$ -chain, at 70 and 196 days of omalizumab treatment, as well as decreased wheal size in response to the allergen [21]. A decrease in receptor numbers then decreases release of mediators and subsequent allergic inflammation [22]. All of the studies on omalizumab's mechanism of action have been performed in atopic patients, and since most patients with chronic urticaria are not atopic, the exact mechanism of omalizumab's action in chronic urticaria is unknown. In the studies of omalizumab in chronic urticaria, the drug is slowly

absorbed, reaching peak concentrations at 7–8 days, and its terminal half-life is 19–22 days [23].

### Clinical efficacy of omalizumab in chronic urticaria

While omalizumab has been FDA approved for treatment of allergic asthma since 2003, the first case report of omalizumab's use in chronic urticaria was not published until 2006. This report noted improvement of cold-induced urticaria in a 12-year-old child after initiation of omalizumab for allergic asthma, with complete resolution of symptoms after 5 months of treatment [24]. The next year, a case series of three patients with chronic idiopathic urticaria was published. Their symptoms previously were resistant to antihistamines and antileukotrienes, but resolved with omalizumab, and two out of the three experienced resolution within 1 week of starting treatment [25]. Following the initial case reports, in 2008, Kaplan's proof-of-concept study examined the use of omalizumab in 12 chronic urticaria patients whose symptoms were refractory to antihistamines [26]. It found that omalizumab administered by asthma dosing tables that adjusted the dose for weight and initial IgE levels (from 75 to 375 mg administered every 2–4 weeks) for 16 weeks resulted in a significant reduction in symptoms, with mean urticaria activity scores dropping from a baseline of 7.5 to 2.6 in the final 4 weeks of treatment [26]. In this study, 58% of patients had complete resolution of symptoms and 92% had some symptom improvement. Rescue medication use decreased and quality of life also improved with treatment. All patients in this study had positive 'autoimmune' markers, defined by a positive autologous serum skin test and basophil histamine release [26].

Two Phase II studies published in 2011 examined the use of omalizumab versus placebo in larger populations of patients with chronic urticaria. In the first, Maurer examined a specific and unusual subset of patients with chronic urticaria who demonstrated IgE autoantibodies to thyroperoxidase and had symptoms refractory to antihistamines [27]. In this study, 49 subjects were treated with either omalizumab or placebo for 24 weeks, with dosing based on asthma dosing tables that adjusted the dose for weight and initial IgE levels (from 75 to 375 mg administered every 2–4 weeks). Of the subjects treated with omalizumab, symptoms measured by the urticarial activity score over 7 days (UAS7) were significantly reduced from baseline compared with placebo (reduction of 17.8 vs 7.9). In addition, 19 out of the 27, or 70% of, subjects treated with omalizumab experienced complete resolution of their urticaria symptoms, compared with one out of 22, or 4.5% of, placebo-treated subjects.

While the two prior studies treated subjects with chronic urticaria with doses of omalizumab based on asthma dosing tables, those tables were developed for an atopic population that typically has elevated IgE levels. Chronic urticaria patients typically have normal IgE levels and the need for adjustment of dosing based on IgE levels was not clear. The second Phase II study published in 2011 was Saini's dose-ranging study of omalizumab in 90 subjects with chronic idiopathic urticaria refractory to antihistamines. This study examined the effect of omalizumab 75, 300, 600 mg or placebo administered as a one-time dose on symptoms 4 weeks later [23]. There was a significant improvement in symptoms at 4 weeks in both the 300- and 600-mg groups, with the 300-mg group reducing urticarial activity scores by 19.9 and the 600-mg group reducing urticarial activity scores by 14.6, both significantly more than the reduction of 6.9 in the placebo group. More than half of the patients in the 300- and 600-mg groups reported a >50% symptom improvement from baseline, and a 100% symptom improvement was noted in 36% of the 300-mg and 28.6% of the 600-mg treatment groups. Furthermore, symptoms improved rapidly within the first 1–2 weeks after administration of omalizumab [23]. It is worth noting that this study did not select for patients with 'autoimmune' urticaria or patients with potentially pathologic IgE, as the prior studies did, but demonstrated efficacy of omalizumab in a general population of chronic urticaria patients. This suggested a broader applicability of this treatment, but optimal dosing and duration of treatment was unknown.

Two Phase III studies examined the use of omalizumab to treat chronic urticaria in larger populations over longer periods of time. Maurer examined the use of omalizumab in 323 patients with chronic urticaria who were symptomatic despite standard doses of H1-antihistamines [28]. This study compared omalizumab 75, 150 and 300 mg to placebo, administered every 4 weeks for 12 weeks (three total injections). There was a significant decrease in itch severity score as well as the weekly urticarial activity score (UAS7) in both the 150- and 300-mg groups. The 150-mg group had a decrease of 8.1 in itch severity score and a decrease of 17.1 in UAS7 from baseline, and the 300-mg group had a decrease of 9.8 in itch severity score and a decrease of 21.8 in UAS7 from baseline. By the end of treatment, 43% in the 150-mg group and 66% in the 300-mg group achieved a minimal symptom level of UAS7 <6. All subjects were followed for an additional 16 weeks after treatment was stopped, and symptom scores gradually increased over time in all groups, and by the end of the follow-up, period scores in the treatment groups were similar to the placebo group's [28]. Kaplan's Phase III

study is the largest and longest published to date, and it assessed the effect of omalizumab 300 mg administered every 4 weeks for 24 weeks (six total injections) in 336 subjects, with a follow-up period of 16 weeks [29]. The population in this study included relatively more severely affected subjects compared with Maurer's study. These subjects had all failed to achieve symptom control with greater than standard H1-antihistamines, plus H2-antihistamines and/or leukotriene receptor antagonists. It demonstrated a significant reduction in itch severity of 8.5 after 12 weeks, with similar effect at 24 weeks. Symptom remission, defined as a UAS7 of 0, occurred in a third of subjects by 12 weeks, and reduction of symptoms to a negligible amount, defined as a UAS7 <6 occurred in half of all patients [29]. During the follow-up period, symptom scores gradually increased, and reached placebo score levels by the end of the 16 weeks of follow-up. This study demonstrated omalizumab's efficacy in a more severely affected population of subjects with chronic urticaria, who had failed second- and third-line treatments.

In addition to clinical efficacy, most of the trials have examined the impact of omalizumab on quality of life, which is an important patient-related outcome in chronic urticaria [30]. Mean Dermatology Quality of Life Index (DQLI) scores significantly improved from baseline to week 12 in Kaplan's 2008 study, and there were statistically significant differences in DQLI between the omalizumab and placebo groups in Maurer's 2011 and 2013 studies, as well as Kaplan's 2013 study [27–29]. Significant changes were also observed in the Skindex 29 and urticaria-specific quality-of-life questionnaire, the Chronic Urticaria Quality of Life Questionnaire (CU-QoL) [27,28]. For a summary of this section, please see [Table 1](#).

### Safety & tolerability of omalizumab

In the published studies on chronic urticaria, omalizumab was generally well tolerated, without serious adverse events compared with placebo. The risk of anaphylaxis with omalizumab is listed as a black-box warning on the US prescribing information for omalizumab, due to 0.1% frequency of anaphylaxis attributed to the medication in premarketing studies and to 0.2% frequency in postmarketing studies on asthma [31]. However, no anaphylactic reactions were reported in the Phase II or III trials [23,27–29]. Furthermore, no patients developed anti-omalizumab antibodies after 40 weeks in Kaplan's study [29]. The omalizumab prescribing information also notes that malignancies occurred with greater frequency in patients treated with omalizumab (0.5%) versus placebo (0.2%) in premarketing studies in asthma, with follow-up generally <1 year [31]. However, no malignancies have been reported in the

| Study (year), Phase                                       | Size | Type of chronic idiopathic urticaria | Prior treatments failed          | Duration               | Dose of omalizumab                                 | Clinical response                                   |                                                                  | Ref. |
|-----------------------------------------------------------|------|--------------------------------------|----------------------------------|------------------------|----------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------|------|
|                                                           |      |                                      |                                  |                        |                                                    | Remission                                           | Significant improvement                                          |      |
| Kaplan <i>et al.</i> (2008), open label, proof of concept | 12   | Autoimmune: + ASST or BHR            | Antihistamines                   | 12 weeks               | Asthma dosing: based on serum IgE level and weight | 58%                                                 | 91%                                                              | [26] |
| Maurer <i>et al.</i> (2011), Phase II <sup>†</sup>        | 49   | Positive IgE-anti-TPO Ab             | Standard dose H1-antihistamines  | 24 weeks               | Asthma dosing                                      | 70 versus 4.5% in placebo                           | Significant reductions in symptoms versus placebo                | [27] |
| Saini <i>et al.</i> (2011), Phase II <sup>†</sup>         | 90   | NA                                   | Standard dose H1-antihistamines  | 4 week f/u to week 16  | 75 mg q4w<br>300 mg q4w<br>600 mg q4w              | 100% improvement: 4.4% <sup>‡</sup><br>36%<br>28.6% | >50% improvement: 52.2%<br>80%<br>57.1%                          | [23] |
| Maurer <i>et al.</i> (2013), Phase III <sup>†</sup>       | 323  | NA                                   | Standard dose H1-antihistamines  | 12 week f/u to week 28 | 75 mg q4w<br>150 mg q4w<br>300 mg q4w              | UAS7 < 6 in: 27% <sup>‡</sup><br>43%<br>66%         | Significant reductions in symptoms in the 150- and 300-mg groups | [28] |
| Kaplan <i>et al.</i> (2013), Phase III <sup>†</sup>       | 336  | NA                                   | H1 and H2 or LTRA antihistamines | 24 week f/u to week 40 | 300 mg q4w                                         | UAS7 < 6 in 50%<br>UAS7 = 0 in 33%                  | Significant reductions in treatment symptoms versus placebo      | [29] |

<sup>†</sup>Double-blind placebo-controlled, parallel studies.

<sup>‡</sup>Not significant versus placebo.

Ab: Antibody; ASST: Autologous serum skin test; BHR: Basophil histamine release; f/u: Follow-up; LTRA: Leukotriene receptor antagonist; NA: Not applicable; q4w: Every 4 weeks; TPO: Thyroperoxidase.

Phase II or III trials in urticaria, including the Kaplan trial, which followed patients for a total of 9 months [29]. In addition, further studies on asthma patients have not supported the initial concern for malignancy risk with use of omalizumab [32]. In a large, unpublished cohort study of patients with asthma, EXCELS, there was a nonsignificant increase in arterial thrombotic events in patients treated with omalizumab versus controls when adjusted for baseline cardiovascular risk, hazard ratio 1.11 (95% CI: 0.70–1.76) and this was also reflected in the analysis of all controlled clinical trials of omalizumab, hazard ratio 1.86 (95% CI: 0.73–4.72), although this was not adjusted for baseline cardiovascular risk [33]. While further epidemiologic study is warranted based on this information, it is notable that no thrombotic events were reported in the studies of omalizumab in chronic urticaria [23,26–29]. In terms of adverse events that were not serious, headache (8.7 vs 3.6%) and upper respiratory tract infections (7.1 vs 2.4%) were more commonly reported while on omalizumab than placebo in the Kaplan study, and headache was more common in the 150-mg omalizumab group than placebo in the Maurer study [28,29].

## Regulatory affairs

Omalizumab was approved in March 2014 both in Europe and in the USA as add-on therapy for the treatment of chronic urticaria in adults and adolescents 12 years and above with inadequate response to H1-antihistamine treatment [11].

## Future research questions

### Long-term treatment

In patients with chronic urticaria that respond to omalizumab, the optimal duration of treatment has not been defined in the published clinical trials. The longest duration of treatment in clinical trials was 24 weeks (six injections), and most subjects' symptoms returned to the levels of the placebo groups by 12–16 weeks after their last injection [28,29]. This suggests that omalizumab is not likely to be 'disease modifying', unlike the effect of cyclosporine, where in one clinical trial, 60% of patients treated for 3 months had continued resolution or significant improvement in their symptoms after discontinuation of treatment [34]. Thus, treatment with omalizumab may be more of a temporizing measure until the chronic urticaria resolves on its own than a disease-modifying treatment. Retrospective analyses have attempted to define the optimal treatment duration with omalizumab and describe the effects of tapering or reducing doses on urticaria symptoms.

In a retrospective review, Song *et al.* reported on 16 patients with chronic urticaria treated with omalizumab 150 mg every 2–4 weeks and followed

up for 9–11 months [35]. This population was a severely affected one, with 13 out of 16 patients having required oral steroids to control their symptoms in the past. In this study, 88% of subjects improved after six injections of omalizumab, with ten out of 16 (62%) achieving remission after one injection, four out of 16 (25%) achieving remission after 2–6 injections, and two patients not improving after two doses and discontinuing treatment. Dosing was spread out to every 6–8 weeks if improvement occurred; however, this resulted in flares of symptoms in two patients. In follow-up, of the 14 patients who achieved initial remission with omalizumab, four patients (29%) remained in remission despite no further omalizumab for 9 months, seven patients (50%) continued on omalizumab with continued control of symptoms, and three (22%) who initially responded to omalizumab developed symptoms refractory to omalizumab [35]. This suggests that a subset of patients may be able to stop omalizumab after a short period of time, but that most patients will need to continue treatment for continued symptom control. It is concerning that in this retrospective, open-label study, a minority of patients who initially responded to omalizumab seemed to become refractory to it, which was not noted in the Phase III clinical trials.

Lefèvre *et al.* retrospectively analyzed 15 patients with chronic urticaria treated with omalizumab 150–300 mg every 4 weeks, who were followed for up to 37 months of treatment [36]. One patient had no improvement after 2 months and stopped, but all others had symptom improvement and were followed for between 2 and 37 months, with an average of 15.53 months of observation. During this time, none of the patients could maintain symptom control with antihistamines or immunosuppressants alone, and symptom scores increased in the week prior to omalizumab administration. This study suggests that treatment for over a year with omalizumab is sufficient to control symptoms, but it does suggest that omalizumab does not cause remission in most patients even after 1.25 years of treatment in most patients. Taken together, these two studies suggest that long-term treatment with omalizumab may help with symptom control in those who initially respond to treatment, but attempts to spread out treatments or stop treatments will generally result in symptom flares.

### Patient-related outcomes

Subjects with chronic urticaria treated with omalizumab have experienced significant improvements in their quality of life in the published trials. Future studies should continue to examine multiple measures

of quality of life including DQLI and CU-QoL, as well as other patient-related outcomes including reductions in antihistamine use and need for corticosteroids.

### Populations to treat

While the clinical trials suggest that omalizumab is an effective treatment for most patients with chronic urticaria, predicting which patients may respond to omalizumab is not possible at this point. A small subset of patients with chronic idiopathic/spontaneous urticaria seems to not respond to omalizumab at all, and how to identify this group of patients is not clear. While the initial proof-of-concept study in 2008 only looked at patients with ‘autoimmune’ urticaria, defined as a positive autologous serum skin test or presence of anti-IgE receptor antibodies, omalizumab’s efficacy is not limited to this subset of patients and the Phase III trials did not report results of these ‘autoimmune’ tests for urticaria. It appears that this is not an important distinction in determining who will respond to treatment among patients with chronic idiopathic/spontaneous urticaria.

The efficacy of omalizumab for physical urticaria is also unclear. While the first case report outlined omalizumab’s success in cold urticaria, the Phase II and III clinical trials have focused on patients with idiopathic/spontaneous chronic urticaria. It is unknown whether the efficacy of omalizumab in these trials translates to patients with primarily physical urticarias. Case reports are conflicting, as there have been case reports that suggested omalizumab reduced symptoms of cold, solar, cholinergic and delayed pressure urticaria, but other case reports have noted lack of improvement of solar and cholinergic urticaria after treatment with omalizumab [37]. Thus, due to lack of quality data, at this point, it is not possible to extrapolate the efficacy of omalizumab in chronic idiopathic/spontaneous urticaria to physical urticaria.

Certain populations have not been included in clinical trials, including pregnant women and children, and the effect of omalizumab is unknown in these populations. Chronic urticaria most commonly affects women in between their 30s and 40s, a time during which childbearing can be a consideration, but the effect of omalizumab on chronic urticaria in women who are trying to conceive, pregnant or nursing has not been studied in clinical trials. There is an ongoing database of women treated with omalizumab for asthma before or during pregnancy, but it does not include women treated for chronic urticaria [38]. Omalizumab has also not been studied in young children with chronic urticaria, as most studies used a cutoff age of 12 or 18 years.

## Conclusion

Chronic urticaria refractory to treatment with antihistamines has been a challenging condition for both patients affected by the disease and physicians treating them, due to the toxicities of second- and third-line treatments and limited data available on them. In the clinical trials published, omalizumab dosed at 300 mg every 4 weeks seems to be an ideal treatment for antihistamine refractory chronic urticaria, with most patients responding to treatment with minimal side effects. In the future, assessment of optimal duration of treatment, as well as the efficacy of omalizumab in subtypes of chronic physical urticarias that were not previously studied and populations previously excluded from clinical trials should help guide further treatment.

## Financial & competing interests disclosure

SC Dreskin receives grant support from the NIH and from Genentech Inc. He serves as a consultant for Genentech Inc. and the Clinical Immunization and Safety Assessment Network (administered by Vanderbilt University). He serves on a Medical Expert Panel for the Division of Vaccine Injury Compensation, Department of Health and Human Services and is a member of a Medical Expert Panel for Vaccine Review for Pfizer Inc. He also serves on the board of the American Board of Allergy and Immunology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

## Executive summary

### Mechanism of action

- Omalizumab (Xolair®, Genentech Inc., CA, USA) is a recombinant humanized monoclonal antibody to IgE.
- Omalizumab binds IgE at the same epitope that binds to the  $\alpha$ -chain of Fc $\epsilon$ RI, the high-affinity IgE receptor, and forms complexes with circulating IgE.
- Omalizumab decreases the availability of IgE to bind to IgE receptors and decreases the expression of high-affinity IgE receptors on mast cells and basophils, decreasing mediator release.
- The exact mechanism of action in chronic urticaria is undefined.

### Pharmacokinetic properties

- Omalizumab is slowly absorbed, reaching peak concentrations at 7–8 days.
- Omalizumab's half-life is 19–22 days.

### Clinical efficacy

- In patients with chronic urticaria refractory to antihistamines, omalizumab decreased urticarial activity scores (itch and hive symptoms) significantly.
- Omalizumab induced remission of symptoms in 30–70% of patients.
- Omalizumab is effective in patients who failed other treatments including high dose H1-antihistamines, leukotriene receptor antagonists and H2-antihistamines.
- Improvement in symptoms occurred in many patients after only one dose.
- Omalizumab is not disease modifying as patients who stopped treatment experienced recurrence of symptoms.
- Omalizumab is effective in patients regardless of autoimmune status.

### Safety & tolerability

- There is no evidence of severe adverse reactions including anaphylaxis or neoplastic disease in clinical trials for urticaria.

### Dosage & administration

- The dosage and administration of omalizumab is a subcutaneous injection of 300 mg every 4 weeks.
- The optimal duration of treatment is unknown.

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