Omalizumab in the Treatment of Urticaria

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Torsten Zuberbier, Tamara Dörr, Clive Grattan, and Marcus Maurer

Core Messages

- Omalizumab, a humanized mouse monoclonal antibody against IgE has been approved for the treatment of urticaria in 2012.
- Having strong evidence on both, efficacy and safety, it is recommended as add-on to antihistamines as third-line treatment option.
- The approved dose of 300 mg subcutaneously every 4 weeks achieves complete control of disease in >40% of patients.
- Response predictors are high IgE at baseline while the presence of autoantibodies may delay response.
- Off-label treatment has shown good efficacy in children as well as CIndU

Omalizumab, an anti-IgE therapeutic antibody, is the first biological licensed for the pharmacotherapy of urticaria. In Europe, in-label use for CSU has been permitted since 2014 although allergologists have had previous experience with this monoclonal humanized antibody as it had been licensed for the use in therapy-resistant allergic asthma for almost a decade longer.

Currently, omalizumab has been licensed for three indications:

1. moderate to severe asthma with proven allergic reaction against a perennial aeroallergen and a reduced lung function (FEV_1 < 80%), frequent daily or nightly symptoms or exacerbations despite daily administration of high-dose inhaled corticosteroids (ICS).

T. Zuberbier · T. Dörr · M. Maurer
Institute for Allergology, Charité – Universitätsmedizin, Berlin, Germany

Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany
e-mail: Torsten.Zuberbier@charite.de; tamara.doerr@charite.de; Marcus.Maurer@charite.de

C. Grattan (✉)
St John's Institute of Dermatology, Guy's Hospital, London, UK
e-mail: Clive.E.Grattan@gstt.nhs.uk

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2. chronic spontaneous urticaria with insufficient symptom relief under standard treatment with H_1-antihistamines.
3. severe chronic rhinosinusitis with nasal polyps (CRSwNP) where the therapy with intranasal corticosteroids does not provide adequate disease control.

12.1 Bioavailability, Metabolism and Elimination

The mean bioavailability of omalizumab after subcutaneous injection is about 62%. Absorption of a single dose happens slowly, the peak serum concentrations being reached 7–8 days after injection. The pharmacokinetics of omalizumab has been shown to be linear in both, asthma and urticaria patients and trough serum concentrations increase proportionally with the dose [1].

Monoclonal antibodies are bound at their Fc receptor binding site by endothelial cells, are then internalized and degraded in the reticuloendothelial system (RES) to smaller proteins and single amino acids, which can then be used for de-novo synthesis of new proteins [2]. Being an IgG antibody, omalizumab is eliminated by the RES of endothelial cells and the liver. The elimination is dose-dependent and clearance of free omalizumab is slower than of omalizumab-IgE complexes or free IgE [3].

Because of its route of elimination, the pharmacokinetics of omalizumab is unlikely to be influenced by renal or hepatic impairment. Also, the genetic polymorphisms of cytochrome P450 enzymes as well as other medication metabolized by them do not interact with the pharmacokinetics of omalizumab.

12.2 Mechanisms of Action of Omalizumab in CSU

Mast cells are the key players in the formation of wheals and angioedema. They express an array of different receptors whose binding to their respective ligand leads to the cell's degranulation, releasing proinflammatory mediators such as histamine, proteases, prostaglandins and leukotrienes, as well as chemokines and cytokines.

Several routes of mast cell activation have been identified to be relevant in the pathogenesis of CSU. Most of them involve the immunoglobulin E (IgE) receptor FcεRI. FcεRI-dependent drivers of mast cell degranulation in CSU include IgE autoantibodies to thyroid peroxidase, interleukin 24 and other autoantigens, IgG and IgM autoantibodies to the alpha chain of FcεRI, and autoantibodies to IgE. Omalizumab is a recombinant DNA-derived humanized immunoglobulin G1κ monoclonal antibody that binds non-receptor bound human IgE [4]. In CSU, omalizumab is understood to prevent mast cell degranulation by decreasing free IgE and reducing the expression of FcεRI receptors.

12.3 Common Adverse Effects

Omalizumab has a favourable risk-benefit ratio with a distinct safety profile. In single doses of up to 4000 mg, no dose-limiting toxicities have been observed. The most commonly reported adverse effects of omalizumab in patients with urticaria include nausea, headaches, swelling of throat or sinuses, cough, joint pain and upper respiratory tract infection [2, 4].

Very rare cases of type I allergic reactions including anaphylaxis to omalizumab have been described. Although they may occur even after a long duration of treatment, the majority of anaphylactic reactions occurred within the first three months of omalizumab treatment [4].

Because of its mechanism of action, one might think that the immune response to parasite and helminth infection would be impaired by omalizumab. This, however, is not the case. Although a slight numerical increase of parasite infections has been reported, the course and duration of the infections were not altered [4].

12.4 Omalizumab in the Treatment of Chronic Spontaneous Urticaria: Clinical Trials

The first randomized controlled multicentre study to show that patients with chronic spontaneous urticaria benefit from the treatment with omalizumab was X-CUISITE [5]. In X-CUISITE, all patients had IgE autoantibodies to thyroid peroxidase, and omalizumab was dosed (75–375 mg) based on body weight and serum IgE levels. At the end of the treatment phase, 70% of patients showed complete control with no more wheals. This is the highest rate of complete responders ever observed in a randomized controlled trial with omalizumab in CSU [6]. The most probable explanation for this high rate of responders is that all patients had autoallergic CSU, which is held to respond well and rapidly to omalizumab treatment.

The proof-of-concept study X-CUISITE was followed by the phase II dose-ranging study MYSTIQUE (75, 300 or 600 mg fixed dose vs. placebo) [6]. MYSTIQUE confirmed the good efficacy and tolerability profile of omalizumab in CSU and was followed by three pivotal Phase III multicentre, randomized, double-blind, placebo-controlled, parallel-group studies in patients with CSU: ASTERIA I, ASTERIA II and GLACIAL [7]. In the ASTERIA studies, patients were treated with 75 mg, 150 mg, 300 mg of omalizumab or placebo every 4 weeks for 6 months (ASTERIA I) or 3 months (ASTERIA II). The GLACIAL study investigated only the 300 mg dose against placebo. All three studies showed a rapid and marked improvement of CSU symptoms: pruritus was significantly reduced in the groups treated with 150 mg or 300 mg dose of omalizumab compared to placebo, significantly more patients became symptom-free after 3 months of 300 mg omalizumab compared to placebo and significant improvements in health-related quality of life were reported for the treatment groups with 150 mg (ASTERIA II) or 300 mg (all studies).

While ASTERIA I and II assessed the efficacy and safety of omalizumab as an add-on therapy in patients who were refractory to licensed doses of H1-antihistamines, GLACIAL assessed the safety of omalizumab as add-on therapy in patients who remained refractory to up to four times the licensed dose of H1-antihistamines plus H2-antihistamines, leukotriene receptor antagonists or both [8–10]. As patients in this study showed poorly controlled CSU despite combination pharmacotherapy, this study population represents the difficult-to-control patients seen in clinical practice more accurately. Based on these studies, EMA and FDA approved omalizumab for the treatment of patients with CSU in 2014.

More recent randomized controlled clinical trials explored the long-term safety and efficacy of omalizumab treatment of patients with CSU, re-treatment efficacy in patients with relapse after stopping omalizumab and the effects of omalizumab on recurrent angioedema in patients with CSU. The X-TEND study demonstrated that omalizumab is effective and safe in patients with CSU treated for 48 weeks [11]. In the OPTIMA study, 9 of 10 patients re-treated with omalizumab after relapse post-withdrawal regained symptomatic control [9]. The X-ACT study showed, in patients with CSU and recurrent angioedema, that omalizumab treatment reduces angioedema burdened days per week threefold versus placebo, with first recurrence of angioedema after 57–63 days with omalizumab and <5 days with placebo [12]. Omalizumab also significantly reduced angioedema-specific quality of life impairment.

Several meta-analyses of the effects of omalizumab in CSU have been performed and published. They all arrive at the conclusion that the evidence provided by randomized controlled clinical trials is of high quality and supports the efficacy and safety of omalizumab in patients with CSU and for treating these patients with 300 mg every 4 weeks.

12.5 Omalizumab in the Treatment of Chronic Spontaneous Urticaria: Real-world Data

In routine clinical practice, the efficacy of omalizumab treatment, in patients with CSU, is similar to that seen in the randomized controlled trials, and often better. In one of the first real life retrospective studies performed, 83% of patients were responders, and 6 and 9 of 10 patients who achieved complete response did so within 1 week and 4 weeks, respectively [13]. In another retrospective study, with 110 CSU patients treated with omalizumab in Spain, 8 of 10 patients showed complete or significant responses [14].

Real life data also supports the efficacy of re-treatment with omalizumab in CSU patients who experience relapse after treatment discontinuation. In one study, where 25 patients with CSU or chronic inducible urticaria stopped omalizumab treatment, all experienced relapse and then received re-treatment with omalizumab. All reported a rapid and complete response within the first 4 weeks, usually during the first days of re-treatment, with no relevant side effects [15]. In another study, 20

patients re-started omalizumab treatment, and complete response was achieved in 18 of them, within 1 week to 2 months [16].

Most CSU patients treated with omalizumab show a fast response, within the first or second month of treatment. Real life studies suggest that a subpopulation of patients takes longer to respond (see Markers for response section). This is in line with the response patterns observed in controlled trials, where some patients who had not responded after 12 weeks of treatment did so after 24 weeks.

It appears to be possible to increase omalizumab dosing intervals, once patients show complete control of their CSU. On the other hand, shortening of dosing intervals or increasing the dose can benefit patients with inadequate response to standard-dosed omalizumab, and it often does. Several recent retrospective studies showed that most patients with partial response to omalizumab treatment experience substantial or complete response when switched to 450 mg/month or 600 mg/month [15]. Experts recommend using higher than standard doses of omalizumab in patients with uncontrolled symptoms throughout the treatment interval and to shorten the interval in patients who show a good response during the beginning and worsening of symptoms at the end of the interval.

Most patients with CSU have recurrent angioedema, with or without wheals. The effects of omalizumab in the latter subpopulation have not yet been investigated in controlled trials. Real life data, i.e. several case reports and case series, support the treatment of CSU with angioedema without wheals, as all reported patients ceased to develop angioedema in response to treatment [17].

The treatment of patients with chronic inducible urticaria without comorbid CSU is off label but may be very effective. A recent systematic review of more than 40 studies including several investigator-initiated randomized controlled trials showed that omalizumab treatment in patients with chronic inducible urticaria results in substantial or complete response in most patients [18]. The supporting evidence for the efficacy of omalizumab treatment of patients with chronic inducible urticaria is strongest for symptomatic dermographism, cold urticaria, solar urticaria and cholinergic urticaria.

Omalizumab is licensed for the treatment of CSU patients who are 12 years old or older. The prevalence and course of CSU in patients younger than 12 years are similar to those in older patients. As of now there are no randomized controlled trials in children under 12 years of age. Real-world data support the efficacy and safety of omalizumab in this age group but are limited. Expert opinion supports the use of omalizumab for the treatment of patients with CSU who are younger than 12 years old, but patients and their parents should understand that this is off label.

CSU, in most patients, shows spontaneous remission after several years duration. It is, therefore, important to assess patients with complete response to omalizumab treatment for the need to continue treatment. This is done by stopping the treatment, often by increasing dosing intervals by one week at a time, and monitoring patients for relapse. Experts recommend doing this after 6 to 12 months of complete response. The authors prefer the latter.

Patients with CSU who do not respond to omalizumab during the first six months of treatment should be considered for treatment with ciclosporin. Real life data and

experience support combining low-dose cyclosporin with omalizumab in patients with CSU who show partial response to omalizumab [17].

A recent meta-analysis of real-world evidence on the safety of omalizumab treatment in adolescent and adult patients with CSU arrived at the conclusion that the safety profile of omalizumab in CSU is similar or superior to that found in clinical trials, where adverse event rates range from 3 to 8% versus 4% in real life [19].

12.6 Markers that Predict and Tools that Help to Monitor Treatment Responses to Omalizumab in Patients with CSU

Based on the current understanding of the pathogenesis of CSU and the mechanisms of action of omalizumab, patients with type I autoimmune (or autoallergic) CSU can be expected to show faster and better responses than those with type IIb autoimmune CSU. This is supported by the results of the X-CUISITE trial, where only patients with type I autoimmune CSU, characterized by the expression of IgE against thyroid peroxidase, were included. Patients in this trial showed very fast onset of responses and a high rate of complete responders, 70%, higher than those observed in other trials, where autoallergy was not an inclusion criterion.

In contrast, patients with type IIb autoimmune CSU, as characterized by a positive autologous serum test or a positive basophil test, show slower onset of response and lower rates of response as compared to patients who are negative for these markers. In one study with 64 patients with CSU, basophil test-positive patients had a median time to response of 29 days, as compared to only 2 days in basophil test-negative patients [19]. In another study, in 41 patients with antihistamine-refractory CSU, a negative basophil test correlated with rates of clinical response to omalizumab: of the 18 patients with a positive test, only 9 (50%) had clinical improvement with omalizumab, whereas 20 of 23 (87%) patients with a negative test were responders [20].

A low total serum IgE level is a marker of type IIb autoimmune CSU and linked to non-response to omalizumab, whereas high normal or elevated total serum IgE levels, a marker of type I autoimmune CSU, are linked to complete response. Markers of type I and IIb autoimmune CSU may, therefore, be helpful to predict treatment responses to omalizumab in patients with CSU.

Treatment responses in CSU patients should be assessed and monitored with the help of validated tools. We recommend using the Urticaria Control Test (UCT) as the primary instrument to do this. The angioedema control test (AECT), the disease activity scores UAS7 and AAS, and the disease-specific quality of life tools CU-Q2oL and AE-QoL should complement the use of UCT whenever possible and as indicated. The decision to change the treatment should be based on the results obtained with these tools using established response criteria. The UCT measures disease control, and 12 or more points indicate that the disease is well controlled, 16 points reflect complete control. The UCT can be used in CSU patients with wheals

who do or do not have angioedema and patients with CIndU. The AECT is used in CSU patients with angioedema, who do or do not have wheals.

12.7 Use in Pregnancy and Breast Feeding

Omalizumab is not licensed for the use in pregnant or lactating women but may be used if it is clinically necessary [1]. Real-world data on the treatment of pregnant and breastfeeding patients with CSU are limited, but they support the notion that omalizumab is effective and safe. Based on these data and the experience with the use of omalizumab in asthma, experts recommend using omalizumab during pregnancy and breastfeeding if indicated after counselling the patient on potential risks and benefits. Although omalizumab crosses the placental barrier, clinical data showed no foetal or neonatal toxicity, and in animal studies, no reproductive toxicity has been observed.

As omalizumab is an IgG antibody, it may be present in human milk and taken orally by the breastfed neonate. IgG is quickly proteolysed in the intestines, and effects on the neonate are not to be expected, which is in line with clinical data.

12.8 Home Therapy

Omalizumab, initially, was available only as a powder for solution, which had to be prepared on-site and vortexed prior to subcutaneous injection. In 2018, the European Commission approved omalizumab self-administration by the use of prefilled syringes, allowing patients with no known history of anaphylaxis to self-inject omalizumab or be injected by a trained lay-caregiver, from the fourth dose onwards, if a physician determines that this is appropriate. This decreases the treatment burden for patients and health care systems.

12.9 Future Developments

Omalizumab is an effective and safe treatment of CSU and most patients benefit from its use. In addition, omalizumab has helped to better understand the pathogenesis of CSU especially the role of IgE and its high affinity receptor. Because of this new IgE and FcεRI-targeted treatments are under development and in clinical testing. The furthest along is ligelizumab. Like omalizumab, ligelizumab (Novartis) is a humanized IgG mAb that binds specific epitopes in the C3 region of IgE and thereby blocks its interaction with FcεRI. Compared to omalizumab, ligelizumab has a higher affinity for IgE and a lower off rate as well as higher efficacy in reducing CSU disease activity. In a recent phase II randomized controlled trial, ligelizumab showed a rapid onset of effects, dose-dependent efficacy and longer time to relapse after treatment discontinuation and a good safety profile [21]. Phase III studies with ligelizumab in adults and adolescents with CSU are ongoing.

The novel long-acting IgE Trap-Fc fusion protein GI-301 (GI Innovation) also binds circulating IgE and shows higher and more durable binding to IgE than omalizumab. GI-301 is also under development for the treatment of CSU.

12.10 Current Positioning of Omalizumab in Local and International Guidelines

Since authorities' approval of omalizumab in the therapy of chronic urticaria, it has become a valuable component of therapy-resistant urticaria internationally.

Despite minor differences, all current guidelines include omalizumab as add-on therapy in antihistamine-refractory chronic spontaneous urticaria as licensed by FDA, EMA and many national authorities such as Swissmedic. While the current guideline on definition, classification, diagnosis and management of urticaria by Zuberbier et al. [22] recommends solely omalizumab as add-on therapy to antihistamines and includes ciclosporin as a further possibility in patients being non-responding to omalizumab or having contraindications or insuperable reservations against subcutaneous injection, the US Practice Parameters guideline [23] recommends omalizumab among other immunomodulating medication (Fig. 12.1). It

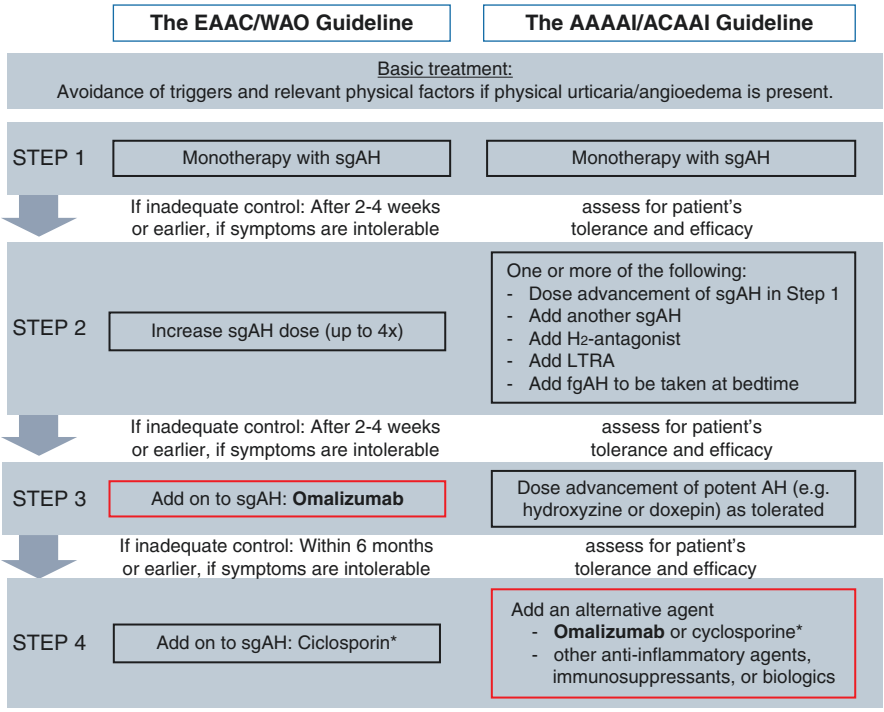

Fig. 12.1 Positioning of omalizumab in the treatment algorithms of the EAACI and the AAAAI Guidelines (Zuberbier T, Bernstein JA: A Comparison of the United States and International Perspective on Chronic Urticaria Guidelines. J Allergy Clin Immunol Pract 2018;6(4):1144–1151.)

should however be noted that the guideline by Zuberbier et al. [24] has been approved by 42 national and international societies representing 94 countries, including the UniUSA. Despite the still lacking authorization of omalizumab in the use of chronic inducible urticaria both guidelines do recommend its use also for those subtypes of chronic urticaria.

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Other Interventions for Chronic Urticaria

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Clive Grattan, Torsten Zuberbier, and Marcus Maurer

Core Messages

- In patients not responding to or having contraindications against the treatment options recommended in the guidelines, several other treatment options with low-quality evidence can be tried.
- Pharmacological interventions include oral corticosteroids, H2 antihistamines, anti-leukotrienes, immunosuppressives and the sulphone anti-inflammatories.
- Non-pharmacological interventions include diet, phototherapy and psychological assessment.

H1 antihistamines and omalizumab are currently the only licensed drugs for the treatment of chronic spontaneous urticaria. This leaves a therapeutic void for chronic urticaria patients who do not respond adequately to antihistamines or for whom omalizumab is either not available or not effective. Historically, many interventions have been used to treat urticaria off licence, most of which are still available and can be valuable for the right patients in the right circumstances. Some drugs are more likely to be effective for specific subtypes or situations and are known as 'targeted' treatments. The evidence base for many of these treatments is based on small studies, case reports, anecdotal reports or clinical experience. Particular care is required when recommending these drugs. Physicians need to be aware of potential side effects, contraindications or interaction with other medications.

Most of these interventions are summarized in Table 9 of the 2018 EAACI/GA²LEN/EDF/WAO guidelines [1]. This chapter aims to summarize the evidence

C. Grattan (✉)
St John's Institute of Dermatology, Guy's Hospital, London, UK
e-mail: Clive.E.Grattan@gstt.nhs.uk

T. Zuberbier · M. Maurer
Institute for Allergology, Charité – Universitätsmedizin, Berlin, Germany

Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany
e-mail: Torsten.Zuberbier@charite.de; Marcus.Maurer@charite.de

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