Omalizumab for Treating Chronic Spontaneous Urticaria: an Expert Review on Efficacy and Safety

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Keywords: Anti-IgE, Chronic Urticaria, Chronic idiopathic urticaria, Chronic spontaneous urticaria, Omalizumab

Abbreviation List: AE, adverse event; AE-QoL angioedema quality of life questionnaire; AH, antihistamine; CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; CU-QoL, chronic urticaria quality of life questionnaire; DLQI, dermatology life quality index; GA²LEN, Global Allergy and Asthma European Network; IgE, immunoglobulin E; IgG, immunoglobulin G; ISS, itch severity score; LTRA, leukotriene receptor antagonist; MAEII, murine anti-IgE antibody moiety; MoA, mode of action; QoL, quality of life; SC, subcutaneous; UAS, urticaria activity score; UAS7, urticaria activity score over 7 days; UCT, urticaria control test.
Abstract

Introduction:
Chronic spontaneous urticaria (CSU) is characterized by the recurrence of itchy hives and/or angioedema for greater than six weeks, with no known external trigger. Omalizumab, a humanized, recombinant, monoclonal anti-IgE antibody, is the only approved add-on therapy for H1-antihistamine refractory CSU patients.

Areas covered:
The objective of this article is to discuss the mechanism of action, pharmacokinetics and pharmacodynamics of omalizumab for the treatment of CSU. The review also summarizes efficacy and safety data from proof-of-concept, Phase II (X-QUISITE, MYSTIQUE), pivotal Phase III (ASTERIA I, ASTERIA II, and GLACIAL), and Phase IV omalizumab studies.

Expert opinion:
Omalizumab is a clinically effective and safe biological therapy for treating H1-antihistamine refractory CSU patients. It significantly reduces CSU symptoms (hives, itch and angioedema), and improves patient health-related quality of life. While omalizumab is already integral to the treatment of antihistamine refractory CSU, widespread use will depend on legal and economic factors, as well as improvements in the early and accurate diagnosis of CSU patients who would benefit from treatment.

1. Introduction
Chronic spontaneous urticaria (CSU), previously known as chronic idiopathic urticaria (CIU), is a common skin condition with an estimated point prevalence of 0.6–1% in the general population [1, 2]. CSU is characterized by the recurrence of itchy hives, angioedema, or both for a minimum of 6 weeks, without any known external trigger [3]. Many patients experience episodes of CSU that persist for longer than one year, and a considerable number of patients are affected for 5 years or more [1]. Furthermore, Curto Barredo and colleagues reported that 25% of patients experienced more than one episode of CSU in their life [4].

Due to the chronic nature of CSU, patients are often medicated for prolonged periods (weeks to years), thus, treatments must be effective and safe for long-term use. The EAACI/GA(2)LEN/EDF/WAO guidelines recommend approved doses of second-generation H1-antihistamines as the first-line treatment for CSU, due to their favorable safety profile, and up to four times the approved dose as the second-line treatment [3, 5, 6]. However, a significant proportion of patients continue to experience symptoms even with high-dose antihistamine treatments and require alternative therapies [1, 7]. Third-line options include add-on therapy with omalizumab (effective; well-tolerated; and licensed for CSU; Box 1), or off-label options montelukast (weak efficacy; well-tolerated; not licensed for CSU) and cyclosporine (effective; poor safety profile; not licensed for CSU) [3]. Short course (< 10 days) corticosteroid may also be used; however, despite their ongoing use worldwide for treating urticaria symptoms (including depot injections), corticosteroids should be avoided due to the risk of severe short-term and long-term adverse effects associated with treatment [8, 9].
Here the development and pharmacology of the biologic therapy omalizumab is described, and clinical efficacy and safety data from omalizumab trials are reviewed. The expert opinion section also provides insight into some of the outstanding research questions, future analyses, social media tools available for patients, and the future of omalizumab for CSU.

2. Development of omalizumab: from asthma treatment to CSU treatment

Omalizumab was originally developed for the treatment of allergic respiratory disorders, as IgE was known to be a major trigger of symptoms [10]. It was first approved for the treatment of moderate-severe persistent asthma in adolescents or adult patients in the US in 2003 [11] and for severe allergic asthma in the EU in 2005 [12]. Shortly after its approval for allergic asthma, real-world evidence emerged suggesting benefits of omalizumab for chronic urticaria (CU) patients who had not responded to conventional treatments [13-16].

Early proof-of-concept data [17-19] and Phase II [20, 21] studies confirmed the efficacy of omalizumab versus placebo in patients with H1-antihistamine refractory CSU. Maurer and colleagues [21] examined the efficacy and safety of omalizumab in CSU patients with immunoglobulin E (IgE) against thyroperoxidase. Omalizumab (75-375 mg, individualized dosage determined using the approved asthma dosing table) significantly reduced weekly urticaria activity scores (UAS7) compared with placebo, with no new safety concerns reported. Initial results indicated that unlike omalizumab treatment for asthma, fixed-dosing may be possible for treating CSU. A second Phase II “dose-finding” study examined the efficacy and safety of a single fixed-dose of omalizumab (75 mg, 300 mg, or 600 mg) or placebo to establish the most effective treatment dose; treatment efficacy peaked at 300 mg and then plateaued [20].
The efficacy and safety of omalizumab (75 mg, 150 mg, and 300 mg) was further confirmed in Phase III clinical trials (Table 1) [22, 23]. Subsequently, omalizumab was approved in the EU (2014) and US (2014) as add-on treatment for CSU patients refractory to H1-antihistamine used at the licensed dose (Box 2; omalizumab practical recommendations) [11, 12]. Omalizumab continues to be the only pharmacological agent licensed for the treatment of H1-antihistamine refractory CSU patients.

**Box 1. Drug summary**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Omalizumab</th>
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**Phase**
- Approved for the treatment of CSU since February 2014 in the EU (EMEA) and March 2014 in the US (FDA)

**Indication in the EU**
- Add-on therapy for the treatment of CSU in adult and adolescent (12 years and above) patients with inadequate response to H1-antihistamine treatment [12].

**Pharmacology description/mechanism of action**
- Recombinant monoclonal anti-IgE antibody that competes for the Cε3 region of the IgE molecule

**Route of administration**
- Subcutaneous injection

**Pivotal trials**
- ASTERIA I [29], ASTERIA II [22], and GLACIAL [23]

*Indication in the US: Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1-antihistamine treatment. Omalizumab is also approved for the treatment of adolescents (≥12 years) and adults with severe allergic asthma since 2003 in the US and 2005 in the EU. It is also approved for the*
treatment of children (≥ 6 years) with uncontrolled allergic asthma (US) or with severe persistent asthma (EU).

CSU, chronic spontaneous urticaria.

3. Omalizumab: mechanism of action, pharmacokinetics and pharmacodynamics

3.1 Mechanism of action

Omalizumab is a humanized, recombinant, monoclonal anti-IgE antibody, which targets circulating IgE. As autoimmune mediated CSU involving anti-IgE autoantibodies does not occur in all CSU patients [24], the mechanism of action of omalizumab in CSU patients remains somewhat elusive.

The omalizumab molecule is comprised of a human immunoglobulin G (IgG) framework and a murine anti-IgE antibody moiety (MAE11; < 5%) that binds to free IgE, irrespective of its antigen specificity, at the site of FcεRI binding, thereby preventing free IgE from binding to FcεRI on mast cells and basophils [25]. Inhibition of IgE-FcεRI binding prevents the activation of the basophils and mast cells, which prevents the release of inflammatory mediators including histamine and pro-inflammatory cytokines [26].

In a recent review, Kaplan et al [27] outlined seven potential mechanisms that may contribute to the efficacy of omalizumab in CSU: decreased free IgE and IgE receptors; reduced mast cell releasability; reversal of basopenia and improved basophil IgE receptor function; reduced activity of IgE autoantibodies against IgE and IgE receptors; reduced activity of intrinsically “abnormal” IgE; reduced activity of IgE autoantibodies against and unknown autoantigen; or a decreased role of coagulation involvement. Their review provides a useful overview of the
existing hypotheses; however, no single theory or combination of theories was found to fully explain the pattern of response seen with omalizumab for CSU patients [27].

3.2 Pharmacokinetics and pharmacodynamics of omalizumab in CSU patients

MYSTIQUE, a Phase II, multicenter, randomized, double-blind, placebo-controlled study assessed the efficacy and safety of omalizumab in 90 patients with moderate-severe CSU who remained symptomatic despite H1-antihistamine treatment [20]. The pharmacodynamic and pharmacokinetic properties of omalizumab reported in the MYSTIQUE trial were similar to those previously reported for asthma patients [11]. Peak omalizumab serum concentrations were reached after an average of 7–8 days following subcutaneous administration and were dose-proportional across the three doses evaluated (75 mg, 300 mg, and 600 mg) [20]. The mean terminal half-life of omalizumab was 19–22 days and apparent clearance averaged 240 mL/day [11, 20, 28]. This slow terminal half-life of omalizumab is due to the slow degradation of the IgG1 framework through Fcγ receptors of the hepatic reticuloendothelial system and sinusoidal endothelial cells [28]. Intact IgG is also excreted through bile [12].

In CSU patients, omalizumab treatment is associated with a dose-dependent increase in the levels of total serum IgE, decreased free IgE, and normalized levels of high-affinity IgE receptor-positive skin mast cells [11, 12]. These cellular changes are associated with reduced hives, itch, and angioedema. Following discontinuation of omalizumab, free serum IgE levels increase and total serum IgE levels decrease towards pre-treatment concentrations.

4. What to expect in terms of efficacy of omalizumab in CSU patients

PubMed and clinicaltrials.gov were used to identify Phase II, Phase III, and Phase IV omalizumab CSU trials (Table 1). The efficacy of add-on omalizumab treatment has been
reported in a number of Phase II (X-QUISITE, MYSTIQUE) [20, 21] and pivotal Phase III clinical trials (ASTERIA I, ASTERIA II, GLACIAL) [22, 23, 29], and in a recent meta-analysis [30]. The three pivotal Phase III trials enrolled patients with moderate-severe CSU/CiU, aged 12–75 years (≥ 18 years in Germany), who continued to experience symptoms despite second generation H1-antihistamine treatment (ASTERIA I and II) or H1-antihistamines at up to 4 times the approved dose plus H2-antihistamines, leukotriene receptor antagonists (LTRAs), or both (GLACIAL) [22, 23, 29]. In the ASTERIA trials, patients were treated with placebo or add-on omalizumab 75 mg, 150 mg, or 300 mg for 12 (ASTERIA II) or 24 (ASTERIA I) weeks [22, 29]. Patients in the GLACIAL trial were treated with placebo or add-on omalizumab 300 mg for 24 weeks [23].

The key efficacy endpoint, reduced mean weekly itch severity score (ISS) at week 12, was achieved in ASTERIA I, ASTERIA II, and GLACIAL. Casale and colleagues [31] reported that a greater proportion of omalizumab (300 mg)-treated patients had well-controlled urticaria symptoms (UAS7 ≤ 6; 52.4–58.8% vs. 12.0–15.1%) or complete symptom control (UAS7 = 0; 33.7–40.0 vs. 4.8–6.9%) at week 12 compared to the placebo arm in GLACIAL and pooled ASTERIA I/II, respectively (Figure 1). The timing of response to omalizumab varied between patients in ASTERIA I, ASTERIA II, and GLACIAL; some CSU patients responded after just one omalizumab 300 mg injection (early responders), while others required 2–6 doses before achieving well-controlled urticaria (late responders) [32]. A meta-analysis of the 7 randomized-controlled CSU trials also confirmed the efficacy of omalizumab 300 mg administered by subcutaneous injection every 4 weeks [30].
In the pooled analysis of phase III data, the 300 mg dose was also reported to be more effective than the 150 mg at reducing mean pruritus scores (primary endpoint) and UAS7 at week 12 (see Figure 1) [31]. Furthermore, in ASTERIA II [22], 150 mg failed to control the angioedema episodes and in ASTERIA I [29], 150 mg failed to control certain quality of life parameters.

4.1. Efficacy of omalizumab at reducing angioedema in CSU patients

Beyond reducing hives and itch in CSU patients, omalizumab 300 mg treatment also significantly increased the proportion of angioedema-free days (91.0–95.8%) in the ASTERIA I/II and GLACIAL trials in comparison to placebo (88.1–88.7%; p < 0.001) [31]. More recently, the X-ACT study (n = 91) confirmed that omalizumab 300 mg reduces angioedema severity and angioedema burden in patients with H1-antihistamine refractory CSU through 28 weeks (Table 1) [33].

4.2. Symptom return after treatment discontinuation and re-treatment

After discontinuing omalizumab (300 mg) treatment, the median time to loss of response was 5 weeks (ASTERIA I and II) to 7 weeks (GLACIAL) [31]. Exploratory analysis of patient data from the ASTERIA I and ASTERIA II suggests that it may be possible to predict fast symptom return based on baseline UAS7 scores and early response to omalizumab treatment [34]. Initial results also suggest that re-treatment with omalizumab is safe and effective for patients who previously responded to treatment [35, 36]. A recent retrospective analysis examined 10 treatment-refractory CU patients who had received omalizumab treatment for longer than 1 year (median of 27 months, range 17–112 months) and had responded to the treatment (8 complete
responders). While being weaned off omalizumab treatment, 5 patients experienced symptom return and required retreatment; retreatment was reported to be safe and effective [37]. The on-going OPTIMA study (NCT02161562) will further investigate the safety and efficacy of omalizumab re-treatment in patients who have relapsed after successful omalizumab treatment (Table 1).

4.3. Long-term efficacy of omalizumab

To date no randomized controlled trials and few retrospective studies have examined the long-term efficacy of omalizumab beyond 24 weeks of treatment. However, in real-life practice, as omalizumab is not a disease modifying agent, we see that many patients with CSU need continuous omalizumab treatment for longer than 6 months.

In a small retrospective analysis of 10 treatment-refractory CU patients, who received omalizumab treatment for longer than 1 year between 2005 and 2015, Har et al., reported good long-term effectiveness of omalizumab. Of the 8 complete omalizumab responders, all 8 remained symptom free for longer than one year without increased dosage, increased dosage frequency, or add-on therapy [37]. Retrospective analysis of 110 treatment-refractory CSU patients treated in 9 Spanish hospitals between 2009 and 2012 also suggests that omalizumab (150 and 300 mg once or twice per month) is effective for long-term use [35]. 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 retreatment. The ongoing XTEND-CSU study will evaluate long-term efficacy and safety in CSU patients treated with omalizumab 300 mg for up to 48 weeks (NCT02392624; Table 1).
**Box 2. Omalizumab: recommendations of use in CSU**

| Dose*          | Licensed dose: 300 mg (EU)  
<table>
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<tr>
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<th>Licensed dose: 300 mg or 150 mg (US)</th>
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<tr>
<td>Frequency#</td>
<td>Every 4 weeks</td>
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<tr>
<td>Route$</td>
<td>SC injection</td>
</tr>
<tr>
<td>Where¥</td>
<td>Divide doses of more than 150 mg among more than one injection site.</td>
</tr>
<tr>
<td>Appearance</td>
<td>Sterile, white, preservative-free, lyophilized powder contained in a single-use vial. Before administration it must be reconstituted with Sterile Water.$</td>
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<tr>
<td>Warnings**</td>
<td>Warnings and precautions include type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock; serum sickness; and parasitic (helminth) infections.</td>
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</table>

*Dosing in CSU is not dependent on serum IgE level or body weight.

*The appropriate duration of therapy for CSU has not been evaluated.

$The injection may take 5–10 seconds to administer because the solution is slightly viscous.

¥Injection site reactions have included swelling, erythema, pain, bruising, itching, bleeding and urticaria. None of the events resulted in study discontinuation or treatment interruption. [11]

£Step by step instructions for reconstituting omalizumab are included in the EMEA summary of product characteristics. [12]

**For further information please see the EMEA summary of product characteristics. [12]

CSU, chronic spontaneous urticaria; SC, subcutaneous.

5. What to expect in terms of safety

The safety (up to 24 weeks) of omalizumab, in combination with second-generation H1-antihistamines (ASTERIA I and ASTERIA II) or H1-antihistamines plus H2-antihistamines, LTRAs, or both (GLACIAL), has been evaluated in all studies. Prior to these CSU studies, the
safety profile of omalizumab was well known from extensive experience treating severe allergic asthma patients. Omalizumab is generally well-tolerated and adverse events (AEs) reported for CSU patients are consistent either with the known omalizumab safety profile in allergic asthma or with CSU-related events observed in the placebo groups [20, 22, 23, 29, 31]. The most common AEs included nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, headache, and cough (Table 2) [31]. Pooled analysis of ASTERIA I/II and GLACIAL showed that the percentage of patients reporting at least one AE was lower in the placebo group (42.6%) than the omalizumab-treated groups (150 mg, 54.9%; 300 mg, 51.0%) at week 12. The majority of AEs reported were of mild to moderate intensity; 6.2% of the placebo group had a severe AE compared to 5.3% of the omalizumab 300 mg group (Table 2). Furthermore, rates of treatment discontinuation due to AEs were higher in the placebo group (5.4%) than in the omalizumab 300 mg (3.6%) or 150 mg (3.4%) group [31].

5.1. Warnings associated with omalizumab
The omalizumab prescribing information contains a warning highlighting the risk of anaphylaxis [11, 12]. Anaphylaxis, which presents as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has occurred in asthma patients after the first dose of omalizumab but also after a long duration of treatment. Most anaphylactic reactions occurred within 2 hours after the first and subsequent injections of omalizumab; however, reactions have been reported beyond 2 hours after the injection [12]. As such, omalizumab must be administered in a healthcare setting and patients should be observed after the injections. It has been reported that a history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following omalizumab administration [12].
There were no reports of omalizumab-related anaphylaxis in the key Phase III trials, ASTERIA I, ASTERIA II, or GLACIAL [31]. However, one case report of anaphylaxis has been reported after omalizumab treatment for CSU; a 37-year-old woman, with no previous history of anaphylaxis, experienced anaphylaxis with a triphasic pattern for up to 36 hours after omalizumab administration [38]. Ertas and colleagues have also reported four cases of angioedema and/or urticaria flare-ups following omalizumab administration for CSU [39]. Omalizumab treatment was discontinued in all four patients; however, it remains unclear whether these flare-ups were due to ineffectiveness of omalizumab or represent an adverse reaction to the treatment.

5.2. Long-term safety in asthma patients

The long-term safety of omalizumab has not been examined in randomized controlled CSU trials. However, as omalizumab has been approved for over a decade for the treatment of severe allergic asthma, clinical trial data and real-world evidence of long-term safety is available [40, 41]. In a recent systematic review of 24 ‘real-life’ asthma studies, Abraham and colleagues reported that omalizumab has a positive short- and long-term safety profile [41]. Retrospective analysis of CSU patients also indicates that omalizumab is safe for long-term use (up to 112 months) [35, 37].

6. Omalizumab improves CSU patients’ quality of life
CSU has a detrimental impact on many aspects of patient quality of life (QoL), such as mood, sleep, and daily activities [42-45]; and is associated with a significant economic and social burden [46-49]. The aim of treatment is rapid and complete symptom control [3], allowing patients to lead a normal work, social, and family life that is unburdened by wheals, itch, or swelling. CSU- and angioedema-specific QoL questionnaires have been developed and validated: the chronic urticaria QoL questionnaire (CU-QoL) and the angioedema QoL questionnaire (AE-QoL), respectively [50-52]. These questionnaires have been used in parallel with the dermatology life quality index (DLQI) to assess CSU-related QoL in clinical trials (Table 1).

Omalizumab 300 mg effectively improved QoL compared with placebo in ASTERIA I, ASTERIA II and GLACIAL. Pooled analysis of ASTERIA I/II and GLACIAL revealed that the mean change in DLQI scores from baseline were 30–50% greater in the omalizumab 300 mg group versus the placebo group [31]. Additionally, results from the X-ACT study have shown that, in H1-antihistamine refractory patients with moderate-severe CSU and angioedema, omalizumab leads to a significant improvement in CU-QoL and AE-QoL [33]. Furthermore, omalizumab treatment is associated with substantial reductions in daytime sleepiness and sleep disruption [53]. Improvement in sleep was reported after the first dose of omalizumab in ASTERIA I, ASTERIA II and GLACIAL. Sleep continued to improve throughout the active treatment period and patients receiving omalizumab 300 mg achieved greater improvement in sleep than those in other treatment groups [45].

7. Expert Opinion
Until recently, CSU remained a poorly understood disease and, for H1-antihistamine refractory CSU patients, approved treatment options were unavailable. Healthcare professionals often perceived these patients as difficult to manage and patients regularly experienced persistent symptoms and impaired QoL. Since the introduction of omalizumab there has been a significant increase in the dissemination of knowledge relating to CSU diagnosis and treatment, and the clinical management of previously difficult-to-treat CSU patients has changed significantly. Validated disease activity and QoL questionnaires [50-52] are now widely available and are frequently used. These tools allow both physicians and patients to monitor QoL and symptom response to omalizumab treatment between patient visits (UAS) or to retrospectively evaluate disease activity prior to commencing treatment (urticaria control test [UCT]) [54].

Omalizumab treatment, for antihistamine-refractory CSU patients, should be consistent with the general objective of treatment defined in the guidelines, i.e. treat the episode of CSU until it is gone (UAS7 = 0). Although it has been suggested that omalizumab be stopped abruptly at this point, in my opinion, if the patient is stable, with a complete remission of signs and symptoms, it may be useful to prolong the time between treatment administrations (increase intervals between omalizumab injections gradually from 4 to 6 to 8 weeks). Furthermore, the baseline UAS7 and initial response to omalizumab should be taken into consideration, as they may be useful predictors of symptom return following treatment discontinuation [34].

Clinical trials and real-world CSU studies have consistently reported significant clinical benefits and favorable safety of omalizumab. Omalizumab demonstrated an impressive improvement in urticaria symptoms compared with antihistamines at licensed dose in the pivotal Phase III trials
[20, 22]. Personal experience and published retrospective data from 118 CSU patients [55] suggest that omalizumab is also more effective than cyclosporine and that treatment-response is more predictable with omalizumab than with alternative third-line treatment options such as methotrexate. Despite the clear benefits of omalizumab treatment versus other third-line options, physician and patient needs will impact whether omalizumab is selected above other third-line options for H1-antihistamine refractory CSU patients. If efficacy and safety are the main priority, omalizumab will be the number one choice; whereas, if the cost-benefit ratio is the key priority then omalizumab will only be prescribed after an accurate analysis of the direct and indirect costs of previous treatments [56]. Information regarding pharmaco-economical evaluation is very limited; however, future results from real-world evidence studies, such as AWARE and ASSURE-CSU, will provide additional information. Country specific regulations and reimbursement criteria also impact whether physicians choose omalizumab above other recommended treatment options.

The introduction of omalizumab has encouraged the development of a range of digital tools and CSU patient platforms. One such tool is the TARGET My Hives mobile application (http://myhives.com/) [57], which facilitates interactions between CSU patients from around the world and allows patients to find urticaria specialists. Other initiatives, such as World Urticaria Day have raised awareness of urticaria and aim to improve the early treatment and diagnosis of CSU. The urticaria day website (http://urticariaday.org) [58] also includes a forum for the urticaria community to discuss their experiences with CSU, and provides links to patient support platforms and networks. Other recent initiatives include the academia-driven open-ended CU registry (CURE; http://www.urticaria-registry.com/) [59], the Global Allergy and Asthma
European Network (GA²LEN) centers of reference and excellence in urticaria (UCAREs), and national urticaria networks, including XUrCB (Catalan-Balear in Spain); AFSAM-UCS (France); and UNEV (Germany). These initiatives aim to improve widespread knowledge of CSU and should allow for earlier and correct diagnosis of patients who would benefit from omalizumab treatment.

Omalizumab is already an integral part of the treatment strategy for H1-antihistamine refractory CSU; however, further analyses are required to complete our understanding of: the mechanism of action of omalizumab in CSU; the predictive value of FcεRI to omalizumab response [60]; the cost-benefit ratio of omalizumab; the safety and efficacy of omalizumab in special populations, such as children, pregnant women, and elderly CSU patients; the safety and efficacy of long-term treatment (beyond 24 weeks), retreatment, and alternative treatment regimens. The efficacy of omalizumab for treating other types of urticaria e.g. chronic inducible urticaria (CIndU) is currently being investigated. Initial evidence presented at the Global Urticaria Forum (GUF) 2016 meeting suggests that omalizumab effectively treats cold urticaria, cholinergic urticaria, solar urticaria, aquagenic urticaria, and dermographism [61, 62, 63]. Ongoing studies will provide answers to a number of these outstanding issues over the coming years (Table 1) and within the next 5 years omalizumab is likely to be used globally to treat H1-antihistamine refractory CSU patients. The widespread use of omalizumab will depend on economic and legal factors, and on the correct identification of CSU patients and improvements in predicting treatment-response. Increased awareness of CSU should reduce delays in patient diagnosis and allow for early identification of patients who would benefit from an effective and safe treatment including H1-antihistamines and omalizumab. Eventually omalizumab may be recommended as
the only third-line therapy for antihistamine-refractory patients in future treatment guidelines, with other effective treatments included as fourth-line options. In fact, in some countries (i.e. Spain or Germany), expert consensus groups have already agreed to recommend omalizumab as the only third-line treatment option above other third-line treatment choices.

Acknowledgements

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Figure 1. Proportion of responders by treatment group in GLACIAL and pooled analysis of ASTERIA I and II. *P < .0001. †P = .002. UAS7, urticaria activity score over 7 days. Reprinted from Casale et al. [31].
Table 1: Omalizumab for the treatment of CSU: drug development program

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Participants</th>
<th>Objective and Intervention</th>
<th>Major outcomes: efficacy, safety, and QoL</th>
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<tr>
<td><strong>Proof-of-concept</strong></td>
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<tr>
<td>Kaplan and colleagues [17]</td>
<td>Single arm, placebo-controlled exploratory proof-of-concept trial of omalizumab, using FDA-approved dosing guidelines for allergic asthma.</td>
<td><strong>Total:</strong> 12 CU patients (18–75 years) with persistent symptoms for ≥ 6 weeks despite treatment.</td>
<td>The efficacy and safety of omalizumab (SC administration of placebo for 4 weeks followed by omalizumab every 2 or 4 weeks for 16 weeks) in CU patients refractory to H1-AH.</td>
<td>Efficacy: Omalizumab reduced UAS from baseline to the final 4 weeks. Overall, 7/12 patients achieved complete control, 4/12 patients responded to omalizumab but urticaria persisted, and 1 patient was a non-responder. Safety: No AEs were observed or reported. QoL: QoL improved over the course of omalizumab treatment (assessed using the DLQI).</td>
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<td><strong>Location</strong> United States</td>
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<td>Gober and colleagues [19]</td>
<td>Double-blind, placebo-controlled trial of omalizumab using FDA-approved dosing guidelines for allergic asthma.</td>
<td><strong>Total:</strong> 20 CSU patients (18–80 years) with active disease despite treatment.</td>
<td>The efficacy and safety of omalizumab (SC injection every 4 weeks for 16 weeks (8 week follow-up) in H1-AH refractory CSU patients.</td>
<td>Efficacy: Omalizumab treatment significantly increased symptom-free days and decreased urticaria severity scores compared to placebo treatment. QoL: QoL improved over the course of treatment (assessed using the Skindex-29).</td>
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<tr>
<td>NCT00130234</td>
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<td>Phase II</td>
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<td>X-QUISITE [21]</td>
<td>A randomized, 24 week, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy and safety of omalizumab in patients with moderate-severe CU who remain symptomatic despite treatment and with IgE against thyroperoxidase (level ≥ 8.0)</td>
<td><strong>Total:</strong> 49 patients (18–70 years)</td>
<td>The efficacy, safety, and tolerability of omalizumab (75 - 375 mg SC administration every 2 or 4 weeks during a 24 week treatment period) were assessed in</td>
<td>Efficacy: Omalizumab had superior efficacy over placebo, as measured by UAS7 scores. Safety: The rate of AE was similar</td>
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<tr>
<td>MYSTIQUE [20] NCT00866788</td>
<td>A Phase II, multicenter, randomized, double-blind, placebo-controlled dose ranging study of omalizumab in patients with CSU who remain symptomatic despite H1-AH treatment.</td>
<td>Total: 90 patients (12–75 years) with moderate-severe CSU despite treatment.</td>
<td>Groups: Omalizumab 600 mg (n = 21) Omalizumab 300 mg (n = 25) Omalizumab 75 mg (n = 23) Placebo (n = 21)</td>
<td>The efficacy and safety of omalizumab (single 75 mg, 300 mg, and 600 mg SC dose; 12 week follow-up) was assessed in H1-AH refractory CSU patients.</td>
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<tr>
<td>MoA study NCT01599637</td>
<td>A Phase II, multi-center, randomized, double-blind, placebo-controlled study to determine the MoA of omalizumab in patients with CSU who remain symptomatic despite H1-AH treatment</td>
<td>Recruitment complete</td>
<td>The MoA of omalizumab (300 mg SC administration every 4 weeks during a 12 week treatment period) was assessed in CSU patients who remain symptomatic despite standard dose H1-AH treatment</td>
<td>Data not yet published</td>
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<tr>
<td>Location</td>
<td>Germany*</td>
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<tr>
<td>Phase III</td>
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<tr>
<td><strong>ASTERIA I [29]</strong></td>
<td><strong>ASTERIA II [22]</strong></td>
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<tr>
<td>NCT01287117</td>
<td>NCT01292473</td>
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<tr>
<td>A global, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab.</td>
<td>A global, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab.</td>
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<tr>
<td><strong>Location</strong></td>
<td>Denmark, France, Germany*, Italy, Poland, Spain, Turkey, United States</td>
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<tr>
<td><strong>Total</strong>: 319 patients (12–75 years) with moderate-severe CSU who remain symptomatic despite H1-AH treatment.</td>
<td><strong>Total</strong>: 323 patients (12–75 years) with moderate-severe CSU who remain symptomatic despite H1-AH treatment.</td>
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<tr>
<td><strong>Groups</strong></td>
<td><strong>Efficacy</strong></td>
<td><strong>Efficacy</strong></td>
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<tr>
<td>Omalizumab 300 mg (n = 81)</td>
<td>The efficacy and safety of add-on omalizumab 300 mg treatment (SC administration every 4 weeks during a 24 week treatment period; 16 week follow-up) was assessed in CSU patients who remain symptomatic despite approved doses of H1-AH.</td>
<td>Dose dependent reductions in weekly ISS and UAS7 were observed with omalizumab 300 mg and 150 mg</td>
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<tr>
<td>GLACIAL [23]</td>
<td>A global, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of omalizumab.</td>
<td><strong>Total:</strong> 335 patients (12–75 years) with moderate-severe CSU despite treatment. <strong>Groups</strong> Omalizumab 300 mg (n = 252) Placebo (n = 83)</td>
<td>The efficacy and safety of add-on omalizumab 300 mg treatment (SC administration every 4 weeks during a 24 week treatment period; 16 week follow-up) was assessed in CSU patients who remain symptomatic despite approved dose H1-AH treatment.</td>
<td>The incidence of common treatment emergent AEs during the treatment period was similar across treatment groups and the frequency of serious AEs was low. The rate of serious AEs was highest in the omalizumab 300 mg group (6%) compared with patients in the omalizumab 75 mg (1%), omalizumab 150 mg (1%) and placebo (3%) groups. No deaths occurred. QoL: Omalizumab 300 and 150 mg treatment led to a significant improvement in QoL versus placebo treatment (assessed using DLQI and CU-QoL).</td>
</tr>
</tbody>
</table>

NCT01264939 | Location  Denmark, France, Germany*, Italy, Poland, Spain, Turkey, United States | **Groups** Omalizumab 300 mg (n = 79) Omalizumab 150 mg (n = 83) Omalizumab 75 mg (n = 82) Placebo (n = 79) | during a 12 week treatment period; 16 week follow-up) was assessed in CSU patients who remain symptomatic despite approved dose H1-AH treatment. | **Efficacy:** For all efficacy endpoints (ISS, UAS7), there was a statistically significant difference in favor of omalizumab 300 mg over placebo. Omalizumab also increased the proportion of angioedema-free days compared with placebo. **Safety:** Incidence and severity of AEs and serious AEs were similar across the treatment groups. Overall, 65.1% of patients in the omalizumab group and 63.9% of patients in the placebo group reported one or more AE during the treatment period. The rate of serious AEs was 7.1% in the omalizumab 300 mg group vs. 6.0% in the placebo group. No deaths occurred. |
### X-ACT [33]  
**NCT01723072**  
- **Trial Type:** A Phase III, randomized, double-blind, placebo-controlled, multicenter trial to investigate the impact of omalizumab on QoL measures as well as the incidence and severity of angioedema.  
- **Location:** Germany  
- **Patients:** Total: 91 patients (18–75 years) with moderate-severe CSU and a history of angioedema despite treatment.  
  - **Groups:**  
    - Omalizumab 300 mg (n = 44)  
    - Placebo (n = 47)  
- **Efficacy:** The impact of add-on omalizumab 300 mg treatment (SC administration every 4 weeks during a 24 week treatment period; 8 week follow-up) on QoL measures and incidence and severity of angioedema was assessed in CSU patients with angioedema despite high-dose H1-AH treatment.  
- **Safety:** Overall, 68.2% of patients in the omalizumab group and 72.3% of patients in the placebo group reported one or more AE. The rate of serious AEs was 9.1% in the omalizumab 300 mg group vs. 4.3% in the placebo group. No deaths occurred.  
- **Quality of Life (QoL):** Omalizumab 300 mg treatment led to a significant improvement in QoL versus placebo treatment (assessed using DLQI and CU-QoL).

### POLARIS  
**NCT02329223**  
- **Trial Type:** A Phase III, multicenter, randomized, double-blind, placebo-controlled parallel-group study to evaluate the efficacy and safety of omalizumab.  
- **Location:** Japan, Republic of Korea  
- **Recruitment Status:** Recruitment complete.  
- **Efficacy:** The efficacy and safety of omalizumab 150 mg, or omalizumab 300 mg every 4 weeks (SC administration) during a 12 week treatment period in patients with CSU who remain symptomatic despite standard-dose H1-AH will be assessed.  
- **QoL:** Omalizumab 300 mg treatment led to a significant improvement in QoL versus placebo (DLQI, AE-QoL, and CU-QoL).  
- **Data Availability:** Data not yet published.

### OPTIMA  
**NCT02161562**  
- **Trial Type:** Phase III, multicenter, randomized, open-label, parallel-assignment efficacy study.  
- **Location:** Study is ongoing (recruiting)  
- **Efficacy:** The efficacy of step-up therapy (150 mg to 300 mg for patients not controlled with 150 mg) and of optimized re-treatment therapy with omalizumab (150 mg or 300 mg) will be assessed.  
- **Data Availability:** Data not available.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Objectives</th>
<th>Location</th>
<th>Status</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina, Brazil, Canada, Chile, Dominican Republic, Guatemala, Mexico, Panama</td>
<td>mg; SC administration every 4 weeks for 20 weeks) after relapse will be assessed in patients with CSU who are clinically well-controlled following their first course of omalizumab treatment.</td>
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<tr>
<td><strong>Phase IV</strong></td>
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<tr>
<td>XTEND-CSU NCT02392624</td>
<td>A Phase IV, multicenter, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of omalizumab through 48 weeks in patients with CSU. Study is ongoing (not recruiting). The long-term (up to 48 week) efficacy of omalizumab 300 mg treatment (SC administration every 4 weeks) will be assessed in CSU patients who remain symptomatic despite H1-AH treatment (up to 4 times the approved dose).</td>
<td>United States</td>
<td>Study is ongoing (not recruiting).</td>
<td>Data not available.</td>
<td></td>
</tr>
<tr>
<td>SUNRISE NCT02550106</td>
<td>A Phase IV, multicenter, single-arm and open-label study with omalizumab in CSU patients who remain symptomatic despite treatment. Completed The efficacy of omalizumab (300 mg every 4 weeks until Week 8) will be assessed in patients with CSU who remain symptomatic despite H1-AH treatment.</td>
<td>France</td>
<td>Completed</td>
<td>Data not available.</td>
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</tr>
</tbody>
</table>

**Retrospective and observational studies: UCREX, ASSURE-CSU and AWARE (in progress)**

*In Germany only patients aged 18 to 75 were recruited.*

AE, adverse event; AE-QoL, angioedema quality of life questionnaire; AH, antihistamine; CSU, chronic spontaneous urticaria; CU-QoL, chronic urticaria quality of life questionnaire; DLQI, dermatology life quality index; ISS, itch severity score; Leukotriene receptor antagonist (LTRAs); MoA, mode of action; QoL, quality of life; SC, subcutaneous; UAS, urticaria activity score; UAS7, urticaria activity score calculated over 7 days.
Table 2: Patients with treatment-emergent adverse events during weeks 1 to 12 of treatment in ASTERIA I, ASTERIA II, and GLACIAL combined

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n = 242)</th>
<th>Omalizumab 150 mg (n = 175)</th>
<th>Omalizumab 300 mg (n = 412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>103 (42.6)</td>
<td>96 (54.9)</td>
<td>210 (51.0)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>8 (3.3)</td>
<td>1 (0.6)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>AEs by severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>41 (16.9)</td>
<td>50 (28.6)</td>
<td>94 (22.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>47 (19.4)</td>
<td>42 (24.0)</td>
<td>91 (22.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>15 (6.2)</td>
<td>3 (1.7)</td>
<td>22 (5.3)</td>
</tr>
<tr>
<td>AEs with incidence ≥3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>44 (18.2)</td>
<td>40 (22.9)</td>
<td>94 (22.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>30 (12.4)</td>
<td>23 (13.1)</td>
<td>63 (15.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17 (7.0)</td>
<td>16 (9.1)</td>
<td>27 (6.6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 (2.1)</td>
<td>2 (1.1)</td>
<td>20 (4.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (2.1)</td>
<td>2 (1.1)</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>14 (5.8)</td>
<td>26 (14.9)</td>
<td>42 (10.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (2.9)</td>
<td>21 (12.0)</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>11 (4.5)</td>
<td>9 (5.1)</td>
<td>29 (7.0)</td>
</tr>
<tr>
<td>Coughing and associated symptoms</td>
<td>3 (1.2)</td>
<td>2 (1.1)</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (1.2)</td>
<td>2 (1.1)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>23 (9.5)</td>
<td>12 (6.9)</td>
<td>45 (10.9)</td>
</tr>
<tr>
<td>Urticarias</td>
<td>12 (5.0)</td>
<td>5 (2.9)</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>Idiopathic urticaria</td>
<td>6 (2.5)</td>
<td>1 (0.6)</td>
<td>9 (2.2)</td>
</tr>
</tbody>
</table>

AE, Adverse event.
Reprinted from Casale et al. [31]
References

   •These guidelines are of interest as they describe the diagnosis and treatment of urticaria


   •This reference is of interest as it is an early proof-of-concept study of omalizumab for the treatment of CU


   •This reference is of interest as it is an early proof-of-concept study of omalizumab for the treatment of CSU/CIU

   •This reference is of interest as it describes the first “dose-finding” phase II study of omalizumab for the treatment of CSU

   •This reference is of interest as it describes the first phase II evaluation of the efficacy and safety of omalizumab for the treatment of CSU

   ••This reference is of considerable interest as it reports phase III efficacy and safety data of omalizumab for the treatment of H1-refractory CSU up to 12 weeks

••This reference is of considerable interest as it reports phase III efficacy and safety data of omalizumab for the treatment of CSU patients refractory to H1-AH treatment (up to four times the approved dose), and either H2 blockers or LTRAs, or all three drugs in combination.


••This reference is of considerable interest as it reports pooled efficacy and safety data from three pivotal phase III studies of omalizumab for the treatment of H1-refractory CSU up to 24 weeks


••This reference is of considerable interest as it reports pooled efficacy and safety data from three pivotal phase III studies of omalizumab for the treatment of CSU


