

# Omalizumab: A Review of Its Use in Patients with Chronic Spontaneous Urticaria

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**Abstract** Omalizumab (Xolair®) is a humanized, recombinant, IgG, anti-IgE monoclonal antibody that binds to the Fc region of free IgE and prevents it from binding to its high-affinity receptor (FcεR1) on mast cells and basophils. This reduction in free IgE leads to a reduction in mast cell/basophil degranulation and the release of histamine, and to the down-regulation of FcεR1 receptors on these cells. Omalizumab does not bind to cell-bound IgE or to IgG. In well-controlled clinical trials in patients with chronic spontaneous urticaria and persistent symptoms despite background treatment with antihistamines, add-on therapy with subcutaneous omalizumab 300 mg every 4 weeks for 12 or 24 weeks significantly reduced the severity of itching, and the number and size of hives, and increased patients' health-related quality of life and the proportion of days free from angioedema compared with placebo. Subcutaneous omalizumab was generally well tolerated; the incidence and severity of adverse events in omalizumab recipients were similar to those in placebo recipients, and most adverse events were of mild or moderate severity. The only adverse events occurring more frequently with omalizumab than with placebo during treatment in a safety study were headache and upper respiratory tract infection. Thus, omalizumab is an

effective and well-tolerated add-on therapy in patients with chronic spontaneous urticaria who are symptomatic despite background therapy with H<sub>1</sub> antihistamines.

## Add-on omalizumab in chronic spontaneous urticaria: a summary

A humanized, recombinant, IgG, anti-IgE monoclonal antibody targeting the Cε3 domain

Binds to free IgE and prevents it from interacting with its high-affinity receptor (FcεR1), leading to reduced histamine release and down-regulation of FcεR1

Significantly more effective than placebo in reducing itch and hives, and increasing health-related quality of life and angioedema-free days

Generally well tolerated, with a tolerability profile similar to that of placebo

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## 1 Introduction

Chronic spontaneous urticaria (CSU) is a skin disorder characterized by the sudden appearance of hives (weals), angioedema, or both, with no identifiable cause, that persists for 6 weeks or longer [1]. The hives generally occur daily, or near-daily, and are transient. Itch is the dominant symptom in most patients that interferes with sleep and daily activities, and negatively impacts on quality of life. However, swelling and pain in those with angioedema may

also have a major negative impact [1]. The incidence of urticaria is almost twofold higher in women than in men and has a peak incidence at 20–40 years of age [2]. It has been estimated that CSU may affect 0.5–1 % of the population at any one time in Europe [2].

The pathogenesis of urticaria is uncertain, but has been associated with histamine release from cutaneous mast cells and blood basophils [3]. A proportion of patients with CSU (about one-third [2]) test positive in the autologous serum skin test, indicating the presence of autoantibodies or histamine-releasing factors, and some patients test positive for IgG autoantibodies to the high-affinity IgE receptor (FcεR1) and/or IgE in the basophil histamine-release assay [4].

Symptomatic treatment with non-sedating H<sub>1</sub> antihistamines has been the mainstay of therapy for chronic urticaria. International consensus guidelines on the management of urticaria recommend the first-line use of non-sedating, second-generation H<sub>1</sub> antihistamines [1]. In patients who do not respond to licensed dosages within 2 weeks, these guidelines recommend that the dosage be increased up to fourfold. If the response is still inadequate after 1–4 further weeks, the guidelines recommend that ciclosporin, omalizumab or the leukotriene antagonist montelukast be added to the treatment regimen. The guidelines recommend short-course (maximum of 10 days) corticosteroid therapy for exacerbations at any time, if required [1].

Omalizumab (Xolair®), an anti-IgE monoclonal antibody, which has been licensed since 2005 in the EU for the treatment of allergic asthma [5], was recently approved in the EU at a dosage of 300 mg subcutaneously every 4 weeks as add-on therapy for the treatment of CSU in adults and adolescents (aged ≥12 years) with inadequate responses to H<sub>1</sub> antihistamine treatment (the only other licensed therapy for CSU in the EU) [6]. This article provides a narrative review of the efficacy and tolerability of omalizumab in the treatment of adults and adolescents with CSU, and overviews its pharmacological properties. Omalizumab is also approved for CSU, with a broader dosage range, in the US, (see Sect. 6); however, the focus of this review is the approved indication in the EU [6].

## 2 Pharmacodynamic Properties

Omalizumab is a humanized (chimeric human-mouse), recombinant DNA-derived, IgG1κ monoclonal antibody, produced in a Chinese hamster ovary cell line, that binds specifically to the Cε3 domain of IgE and does not bind to IgG [6]. The Cε3 domain is the site at which IgE binds to FcεR1 on mast cells and basophils. Thus, omalizumab binds to free IgE and prevents it from binding to its

receptor on mast cells and basophils; it does not bind to cell-bound IgE [7]. The immune complexes formed between omalizumab and free IgE are physically small, not exceeding one million Daltons in molecular weight [6]. As a result of binding free IgE, the allergic cascade is reduced and FcεR1 on cells are down-regulated in atopic patients treated with omalizumab. Exactly how these actions translate to improvements in CSU symptoms is not clearly understood [6]. It has been hypothesized that autoreactivity may play a larger role in CSU than previously thought, including in patients without a detectable autoimmune cause [3]. Monomeric IgE is able to augment mast cell activity and it has been suggested that levels of autoantibodies too low to be detected in immunoassays may be sufficient to bind to and cross-link receptor-bound IgE and thereby prime mast cells for activation. Depletion of free IgE by omalizumab, with subsequent down-regulation of FcεR1 and CD23 (FcεRII; low-affinity IgE receptor), as well as possible sequestration of incoming allergen molecules by omalizumab-IgE immune complexes, may abolish the ability of IgE to potentiate mast cell activity in this way [3].

The phase II, dose-ranging MYSTIQUE study (*n* = 90), which assessed the efficacy of single-dose omalizumab 75, 300 and 600 mg compared with placebo over 4 weeks (plus 12 weeks of follow-up) in adolescents and adults (aged 12–75 years) with CSU unresponsive to approved dosages of H<sub>1</sub> antihistamines, demonstrated that the 300 mg single dose produced greater responses than the 75 and 600 mg single doses for all efficacy endpoints in the intent-to-treat (ITT) population [8]. Single-dose omalizumab 300 mg was superior to placebo for mean change from baseline to week 4 in urticaria activity score (UAS) over 7 days (UAS7) [primary endpoint] (−19.9 vs. −6.9, *p* < 0.001), weekly itch severity score (ISS) [−9.2 vs. −3.5, *p* < 0.001] and weekly hive score (−10.7 vs. −3.5, *p* < 0.001) [8].

The proof-of-concept X-CUISITE study (*n* = 49) demonstrated that subcutaneous omalizumab for 24 weeks was effective in a subgroup of CSU patients (aged 18–70 years) unresponsive to approved dosages of H<sub>1</sub> antihistamines and with IgE autoantibodies to thyroperoxidase [9]. The study used individualized doses (omalizumab 75–375 mg every 2 or 4 weeks) according to the recommended dosages for allergic asthma, based on baseline serum total IgE levels and body weight [9]. The change from baseline to week 24 in least squares mean UAS7 was significantly greater in omalizumab than placebo recipients (−17.8 vs. −7.9; *p* < 0.01). At week 24, 59 % of omalizumab recipients compared with 14 % of placebo recipients judged themselves to be free of symptoms, while, according to the investigator's global assessment, 67 % of omalizumab recipients achieved

complete resolution of urticaria-related symptoms compared with 4 % of placebo recipients [9]. Percentage improvement in health-related quality of life was significantly greater in omalizumab recipients than in placebo recipients as assessed by the Dermatology Life Quality Index (DLQI) [62 vs. 15 %], Skindex-29 (50 vs. 6 %) and Chronic Urticaria Quality of Life (53 vs. 6 %) questionnaires [9].

In patients with CSU treated with omalizumab, maximal suppression of serum free IgE levels was observed 3 days after the first subcutaneous dose [6]. During 4-weekly repeat dosing, the trough (pre-dose) free IgE levels remained stable between weeks 12 and 24, and then increased to pre-treatment levels during a 16-week follow-up period after stopping therapy [6].

Retrospective assessment of 26 patients who responded to treatment with omalizumab for 16 weeks found that those who maintained remission at 3 months after stopping treatment ( $n = 18$ ) had lower IgE levels (140 vs. 440 [units not stated, but presumably IU/mL];  $p = 0.039$ ) and higher eosinophil levels (227 vs. 96 [units not stated, but presumably cells/ $\mu$ L];  $p = 0.044$ ) than those who relapsed within 3 months ( $n = 8$ ) [reported as an abstract] [10].

### 3 Pharmacokinetic Properties

The average absolute bioavailability of omalizumab after subcutaneous administration is 62 % [6]. Peak serum concentrations are attained on average 6–8 days after subcutaneous administration of a single dose [6]. The pharmacokinetics of omalizumab are linear at doses  $>0.5$  mg/kg [6, 8]. The apparent volume of distribution is 78 mL/kg [6].

Omalizumab is eliminated via the same processes as endogenous IgG, as well as via specific binding and complex formation with IgE [6]. IgG is generally eliminated by the liver, principally by intracellular degradation following endocytosis (e.g. by cells of the reticuloendothelial system) [11]. Intact IgG is also eliminated in the bile [6]. The terminal elimination half-life of omalizumab was estimated by population pharmacokinetic simulations to be 24 days at steady state and the apparent clearance was 3 mL/kg/day for a patient weighing 80 kg [6].

Population pharmacokinetic modelling suggests that, in the treatment of patients with CSU, there is no need for dosage adjustment based on age, race/ethnicity, sex, body weight, baseline IgE levels, autoantibodies to Fc $\epsilon$ R1, or concomitant therapy with H<sub>2</sub> antihistamines or leukotriene receptor antagonists [6]. The pharmacokinetics of omalizumab have not been studied in CSU patients with renal or hepatic impairment [6].

### 4 Therapeutic Efficacy

The efficacy of add-on therapy with omalizumab administered subcutaneously every 4 weeks in the treatment of patients with CSU has been assessed in three fully published, phase III, multicentre, randomized, double-blind, placebo-controlled trials (ASTERIA I [12], ASTERIA II [13] and GLACIAL [14]). The trials enrolled adolescent and adult patients (aged 12–75 years) with chronic disease ( $\geq 6$ -month history) who were symptomatic despite current H<sub>1</sub> antihistamine [12, 13] or combined antihistamine/leukotriene receptor antagonist therapy [14].

Enrolled patients were required to have hives associated with itching for  $\geq 8$  [12, 13] or  $\geq 6$  [14] consecutive weeks prior to enrolment and a UAS7 of  $\geq 16$  and a weekly ISS of  $\geq 8$  during the 7 days prior to randomization. Patients had to have been taking an approved dose of H<sub>1</sub> antihistamines [12, 13] or H<sub>1</sub> antihistamines (up to 4 times the approved dose) plus H<sub>2</sub> antihistamines and/or leukotriene receptor antagonists [14] for  $\geq 3$  consecutive days prior to the screening visit 2 weeks before randomization. Throughout the 12-week primary assessment period, patients maintained stable dosages of their pre-randomization H<sub>1</sub> antihistamine [12, 13] or combination antihistamine/leukotriene receptor antagonist therapy [14].

Patients received a subcutaneous injection of omalizumab 300 mg or placebo every 4 weeks for 12 [13] or 24 [12, 14] weeks and were then followed for an additional 16 weeks post-treatment. In the two dose-ranging, phase III trials (ASTERIA I and II, assessing omalizumab 75, 150 and 300 mg) [12, 13] and the phase II MYSTIQUE study (assessing single-dose omalizumab 75–600 mg) [8] (see Sect. 2), a dose-response relationship with omalizumab was observed, with the 300 mg dose demonstrating the greatest efficacy compared with placebo for all efficacy endpoints. Therefore, only the results for the EU-approved 300 mg dose (see Sect. 6) in the phase III trials are discussed.

The primary endpoint in the ASTERIA I and II studies, and a key efficacy endpoint in the GLACIAL study, was the change from baseline to week 12 in the weekly ISS in the modified ITT (mITT) population (defined as all randomized patients who received at least one dose of study drug) [12–14]. The weekly ISS is the sum of the daily ISS [0 = none, 1 = mild, 2 = moderate and 3 = severe itching] for the previous 7 consecutive days and is measured on a scale of 0–21; the minimally important difference (MID) is 5 or more [12, 13]. The GLACIAL study in patients with refractory disease despite multiple background therapy was primarily designed to assess the safety of omalizumab; all efficacy assessments were secondary endpoints [14].

Secondary efficacy endpoints, all assessed at week 12, consisted of the change from baseline in the UAS7, the weekly number of hives score, the weekly size of the

largest hive score and the DLQI score, as well as the time to MID response in the weekly ISS, the proportion of patients with UAS7  $\leq 6$  or UAS7 equal to zero (post hoc analysis only in ASTERIA II), the proportion of angioedema-free days and the proportion of weekly ISS MID responders [12–14]. The weekly number of hives score is the sum of the daily scores (0 = none, 1 = 1–6, 2 = 7–12 and 3  $\geq 12$  hives) over 7 days (score range 0–21), with a MID of 5.0–5.5. The UAS (score range 0–6) is the sum of the daily ISS and the daily number of hives score. The UAS7 (score range 0–42) is the sum of the UAS over 7 days; the MID is 9.5–10.5. The weekly size of the largest hive score is the sum of the daily scores (0 = none, 1  $\leq 1.25$ , 2 = 1.25–2.5 and 3  $\geq 2.5$  cm) over 7 days (score range 0–21) and has a MID of 4.5–5.0 [12–14].

The mean change from baseline to week 12 in the weekly ISS (primary or key endpoint) was significantly ( $p < 0.001$ ) greater in patients receiving omalizumab 300 mg every 4 weeks than in those receiving placebo in all three phase III trials (see Table 1) [12–14]. The median time to MID response in the weekly ISS was significantly ( $p < 0.001$ ) shorter with omalizumab 300 mg every 4 weeks than with placebo in all three trials (Table 1). In ASTERIA I and GLACIAL, the significant improvement in ISS with omalizumab 300 mg compared with placebo observed at 12 weeks was maintained throughout treatment to 24 weeks [12, 14]. During the 16-week post-treatment follow-up period, weekly ISS values in omalizumab 300 mg recipients in all three trials increased to levels similar to those in placebo recipients, but did not return to baseline values [12–14].

Omalizumab recipients had significantly greater responses than placebo recipients for all secondary efficacy endpoints analysed statistically in ASTERIA I (all  $p < 0.0001$ ), ASTERIA II ( $p < 0.05$ – $0.001$ ) and GLACIAL (all  $p < 0.001$ ) [results for all except change from baseline in weekly size of largest hive score and proportion of weekly ISS MID responders are shown in Table 1] [12–14]. Of note, complete UAS7 responses (i.e. UAS7 = 0 at week 12) were seen in 34–44 % of omalizumab recipients across the three trials compared with 5–9 % of placebo recipients [12–14].

## 5 Tolerability

Data on the tolerability of omalizumab 300 mg every 4 weeks in patients with CSU derive from the phase III trials discussed in Sect. 4 [12–14], particularly the GLACIAL trial [14], which primarily assessed safety and tolerability in highly refractory patients.

Similar proportions of patients receiving omalizumab 300 mg every 4 weeks or placebo experienced at least one

**Table 1** Efficacy of subcutaneous omalizumab in patients with chronic spontaneous urticaria. Results from phase III, randomized, double-blind, placebo-controlled, multicentre trials

| Study (treatment duration; weeks) | Treatment      | No. of pts (mITT) | Mean change from baseline to week 12 [baseline value] |                        |                 | Mean angioedema-free days (%) from weeks 4–12 | Median time to MID response in weekly ISS (weeks) <sup>a</sup> | Percentage of pts at week 12 with: |                   |
|-----------------------------------|----------------|-------------------|-------------------------------------------------------|------------------------|-----------------|-----------------------------------------------|----------------------------------------------------------------|------------------------------------|-------------------|
|                                   |                |                   | Weekly ISS <sup>b</sup>                               | Weekly no. hives score | UAS7            |                                               |                                                                | UAS7 $\leq 6$                      | UAS7 = 0          |
| ASTERIA I [12] (24)               | OMA 300 mg q4w | 81                | −9.4*** [14.2]                                        | −11.4*** [17.1]        | −20.8*** [31.3] | 96.1***                                       | 1.0***                                                         | 51.9***                            | 35.8***           |
|                                   | PL             | 80                | −3.6 [14.4]                                           | −4.4 [16.7]            | −8.0 [31.1]     | 88.2                                          | 4.0                                                            | 11.3                               | 8.8               |
| ASTERIA II [13] (12)              | OMA 300 mg q4w | 79                | −9.8** [13.7]                                         | −12.0** [15.8]         | −21.7* [29.5]   | 95.5**                                        | 1.0**                                                          | 65.8**                             | 44.3 <sup>c</sup> |
|                                   | PL             | 79                | −5.1 [14.0]                                           | −5.2 [17.0]            | −10.4 [31.0]    | 89.2                                          | 4.0                                                            | 19.0                               | 5.1               |
| GLACIAL [14] (24)                 | OMA 300 mg q4w | 252               | −8.6** [14.0]                                         | −10.5** [17.1]         | −19.0** [31.2]  | 91.0**                                        | 2.0**                                                          | 52.4**                             | 33.7**            |
|                                   | PL             | 83                | −4.0 [13.8]                                           | −4.5 [16.4]            | −8.5 [30.2]     | 88.1                                          | 5.0                                                            | 12.0                               | 4.8               |

DLQI Dermatology Life Quality Index, ISS itch severity score, MID minimally important difference, mITT modified intent-to-treat population, NR not reported, OMA omalizumab, PL placebo, pts patients, q4w every 4 weeks, UAS7 urticaria activity score over 7 days

\*  $p < 0.05$ , \*\*  $p < 0.001$ , \*\*\*  $p < 0.0001$  vs. PL

<sup>a</sup> The MID for weekly ISS was a reduction from baseline of  $\geq 5$  points

<sup>b</sup> Primary endpoint in ASTERIA I and ASTERIA II (safety was the primary endpoint of the GLACIAL trial)

<sup>c</sup> Post hoc analysis (no formal statistical analysis plan)

adverse event during the treatment period (12 or 24 weeks) or 16-week follow-up period in ASTERIA I (70.4 vs. 66.3 %) [12], ASTERIA II (64.6 vs. 60.8 %) [13] and GLACIAL (83.7 vs. 78.3 %) [14]. Most adverse events were of mild or moderate severity; severe events occurred in 8 % of omalizumab 300 mg recipients and 9 % of placebo recipients in ASTERIA II [13]. The proportions of patients experiencing serious adverse events with omalizumab 300 mg versus placebo occurring during the treatment period were 0 versus 5.0 % in ASTERIA I [12], 2.5 versus 2.5 % in ASTERIA II [13] and 2.8 versus 3.6 % in GLACIAL [14], while the proportions experiencing serious adverse events during the total study period were 2.5 versus 6.3 % in ASTERIA I [12], 6.3 versus 2.5 % in ASTERIA II [13] and 7.1 versus 6.0 % in GLACIAL [14]. The proportions of patients withdrawing from treatment as a result of adverse events with omalizumab 300 mg versus placebo were 2.5 versus 8.8 % in ASTERIA I [12], 0 versus 0 % in ASTERIA II [13] and 1.2 versus 1.2 % in GLACIAL [14]. There were no deaths in any of the three phase III trials.

The most frequent adverse events by organ class occurring during treatment with omalizumab 300 mg or placebo in the GLACIAL trial were infections and infestations (36.9 vs. 30.1 %), skin and subcutaneous tissue disorders (16.7 vs. 14.5 %), gastrointestinal disorders (15.9 vs. 14.5 %) and nervous system disorders (15.5 vs. 12.0 %) [14]. The most common individual treatment-emergent adverse events occurring during the treatment period with

omalizumab 300 mg were headache, nasopharyngitis, sinusitis and upper respiratory tract infection, with headache and upper respiratory tract infection occurring numerically more commonly in the omalizumab group than in the placebo group [14] (Fig. 1). Upper respiratory tract infections, urinary tract infections and idiopathic urticaria occurred numerically more frequently in the omalizumab group than the placebo group during the 16-week follow-up period [14].

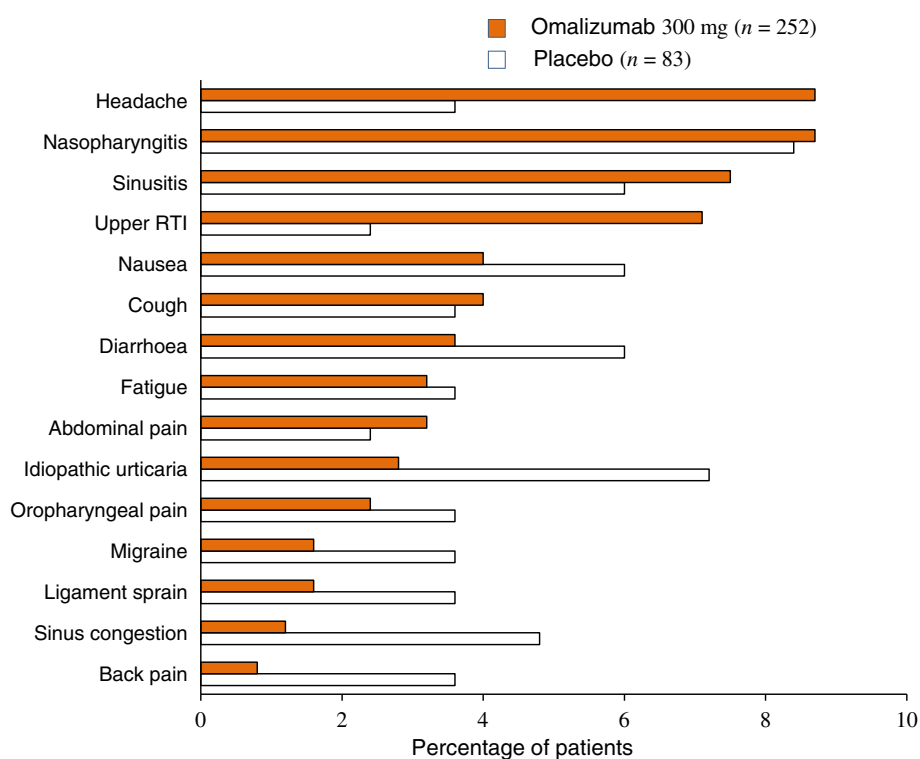
In a pooled analysis of the three phase III trials, adverse events occurring during the 12-week treatment period with an incidence of  $\geq 1$  % in either group and  $\geq 2$  % more frequently with omalizumab 300 mg than with placebo were sinusitis (4.9 vs. 2.1 %), headache (6.1 vs. 2.9 %), arthralgia (2.9 vs. 0.4 %) and injection-site reaction (2.7 vs. 0.8 %) [6].

In phase III trials, there were no new safety concerns relative to the known tolerability profile of omalizumab derived from its use in treating allergic asthma [12, 14]. There were no anaphylactic reactions or clinically relevant changes in laboratory parameters [12–14]. There were no anti-omalizumab antibodies detected at week 40 in the GLACIAL trial [14].

## 6 Dosage and Administration

Omalizumab is indicated in the EU as add-on therapy for the treatment of CSU in adults and adolescents (aged

**Fig. 1** Tolerability profile of omalizumab 300 mg every 4 weeks. Treatment-emergent adverse events of any grade occurring in  $\geq 3$  % of patients in either group during the 24-week treatment period of the GLACIAL trial [14]. RTI respiratory tract infection



$\geq 12$  years) with inadequate response to  $H_1$  antihistamine treatment [6]. The recommended dosage of omalizumab is 300 mg every 4 weeks administered subcutaneously by a healthcare provider. Clinical experience beyond 24 weeks of therapy in the treatment of CSU is limited [6].

Omalizumab is also approved in the US (at 150 or 300 mg subcutaneously every 4 weeks) for the same patient group as in the EU [15]. While some patients respond to the 150 mg dose, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) approved only the 300 mg dose on the basis that there were no apparent safety issues with the 300 mg dose and there was no way to identify which patients would respond adequately to the lower 150 mg dose; therefore, the 300 mg every 4 weeks dosage was considered to provide the optimum benefit-risk profile [16]. In addition, the CHMP considered that patients with angioedema and those with a body weight  $>80$  kg required the 300 mg dose [16].

No dosage adjustment is considered necessary in elderly patients aged  $>65$  years with CSU, although experience in these patients is limited [6]. Omalizumab has not been studied in children with CSU aged  $<12$  years. Since omalizumab is largely cleared by the reticuloendothelial system, renal and hepatic impairment are not considered likely to affect the clearance of omalizumab. However, the effects of renal or hepatic dysfunction on the pharmacokinetics of omalizumab have not been studied and so caution is recommended in patients with renal or hepatic impairment [6].

Local prescribing information should be consulted for details, including warnings, precautions and contraindications.

## 7 Current Status of Omalizumab in Chronic Spontaneous Urticaria

The symptoms of CSU are not known to be inducible and, historically, treatment has been symptomatic [1]. Since histamine release from mast cells and basophils has long been associated with the pathogenesis of CSU,  $H_1$  antihistamines have formed the initial backbone of therapy [1, 17]. However, even when used at four times the licensed dosage, a sizeable proportion of patients fail to respond adequately to  $H_1$  antihistamine therapy. Approximately one-third of patients with CSU produce IgG autoantibodies against IgE or Fc $\epsilon$ R1 [2, 4], and cross-linking of autoantibodies bound to Fc $\epsilon$ R1 leads to degranulation of mast cells and basophils, and the release of histamine. While the mechanism of action of omalizumab in CSU has not been determined, the anti-IgE monoclonal antibody reduces the level of free IgE and results in the down-regulation of Fc $\epsilon$ R1 leading to a reduction in the release of histamine and/or other mediators from mast cells and basophils.

Maximal suppression of free IgE in serum occurs 3 days after subcutaneous administration of omalizumab and IgE levels remain suppressed throughout treatment with omalizumab administered every 4 weeks (Sect. 2).

In well-controlled clinical trials, add-on therapy with subcutaneous omalizumab 300 mg administered every 4 weeks reduced the weekly ISS from baseline (the primary efficacy endpoint) significantly more than placebo in patients with CSU and an inadequate response to  $H_1$  antihistamine, or a combination of high-dose  $H_1$  antihistamine plus either an  $H_2$  antihistamine or a leukotriene receptor antagonist, or both (Sect. 4). In addition, omalizumab 300 mg every 4 weeks significantly reduced the number and size of hives, significantly increased the proportion of days in which patients were free of angioedema and significantly improved patients' health-related quality of life as measured with the DLQI questionnaire. Complete responses for itch severity and number of hives (i.e. UAS7 equal to zero) were observed in at least one-third of patients during treatment. Improvement in symptoms was consistently maintained throughout treatment for up to 24 weeks. Once treatment was stopped, the mean severity of itching and the number of hives gradually increased back to the same levels as those seen with placebo over a period of about 8–16 weeks, although not back to baseline levels (Sect. 4). Most, but not all, patients with CSU experience benefit with omalizumab therapy and there are no predictive factors, including the autologous serum skin test, that can identify those likely to respond [18].

Omalizumab was generally well tolerated as add-on therapy; the incidence and severity of adverse events overall and of serious adverse events with omalizumab 300 mg were similar to those with placebo in all three phase III trials (Sect. 5). This was particularly noteworthy in the safety trial (GLACIAL), which enrolled patients with persistent symptoms despite treatment with multiple background therapies. The incidence of serious adverse events in GLACIAL was numerically lower with omalizumab than with placebo, while the incidence of treatment withdrawal as a result of adverse events with omalizumab was the same as with placebo (Sect. 5). The only adverse events that occurred with a numerically higher incidence with omalizumab 300 mg than with placebo during the treatment period in the GLACIAL trial were headache and upper respiratory tract infection. Compared with the known tolerability profile of omalizumab observed in patients with allergic asthma, the use of omalizumab to treat CSU did not generate any new safety signals. Antibodies directed against omalizumab have been detected in patients treated with omalizumab for allergic asthma [6], but anti-omalizumab antibodies were not detected in the GLACIAL trial.

In conclusion, omalizumab has been shown to be an effective and well-tolerated add-on therapy in patients with CSU unresponsive to H<sub>1</sub> antihistamines.

**Data selection sources:** Relevant medical literature (including published and unpublished data) on omalizumab was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 3 September 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.

**Search terms:** Omalizumab, urticarial, chronic idiopathic urticaria, chronic spontaneous urticaria.

**Study selection:** Studies in patients with chronic spontaneous urticaria who received omalizumab. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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## References

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69(7):868–87.
2. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA<sup>2</sup>LEN task force report. *Allergy*. 2011;66(3):317–30.
3. Chang TW, Chen C, Lin CJ, et al. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2014. doi:10.1016/j.jaci.2014.04.036.
4. Sabroe RA, Grattan CE, Francis DM, et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol*. 1999;140(3):446–52.
5. McKeage K. Omalizumab: a review of its use in patients with severe persistent allergic asthma. *Drugs*. 2013;73(11):1197–212.
6. European Medicines Agency. Xolair 150 mg powder/solution: summary of product characteristics. 2014. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000606/WC500057298.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf). Accessed 3 Sep 2014.
7. Metz M, Maurer M. Omalizumab in chronic urticaria. *Curr Opin Allergy Clin Immunol*. 2012;12(4):406–11.
8. Saini S, Rosen KE, Hsieh H-J, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H<sub>1</sub>-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128(3):567–73.e1.
9. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202–9.e5.
10. Shin B, Kwon HS, Park SY, et al. Blood immunoglobulin E and eosinophil levels predict treatment response to omalizumab in refractory chronic urticaria [abstract no. P6-160]. *Allergy*. 2013;68(Suppl 98):36.
11. Keizer RJ, Huitema AD, Schellens JH, et al. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet*. 2010;49(8):493–507.
12. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H<sub>1</sub> antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2014;. doi:10.1038/jid.2014.306.
13. Maurer M, Rosen K, Hsieh H-J, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. [Erratum appears in *N Engl J Med*. 2013, 368(24), pp. 2340–1]. *N Engl J Med*. 2013;368(10):924–35.
14. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132(1):101–9.
15. US FDA. Xolair (omalizumab): US prescribing information. 2003. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/103976s5211bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103976s5211bl.pdf). Accessed 3 Sep 2014.
16. European Medicines Agency. Xolair (omalizumab) type II variation: assessment report. 2013. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Assessment\\_Report\\_-\\_Variation/human/000606/WC500164453.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000606/WC500164453.pdf). Accessed 3 Sep 2014.
17. Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol*. 2007;157(6):1116–23.
18. Lang DM. A critical appraisal of omalizumab as a therapeutic option for chronic refractory urticaria/angioedema. *Ann Allergy Asthma Immunol*. 2014;112(4):276–9.