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Received Date : 10-Aug-2016

Revised Date : 29-Nov-2016

Accepted Date : 10-Jan-2017

Article type : Review of Therapeutics

Omalizumab for the Treatment of Chronic Idiopathic Urticaria: Systematic Review of the Literature

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Key words: Anti-IgE antibody; chronic idiopathic urticaria; chronic spontaneous urticaria; omalizumab; urticaria

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/phar.1915

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Funding: The authors declare they have no funding sources for this research.

Conflicts of interest: The authors declare they have no conflicts of interest for this research.

Running head: Omalizumab for treatment of chronic idiopathic urticaria

Abstract

Omalizumab is recombinant humanized monoclonal antibody to immunoglobulin E. Guidelines for the treatment of chronic idiopathic urticaria (also known as chronic spontaneous urticaria) recommend the use of omalizumab as third-line therapy in addition to high doses of histamine receptor type 1 (H₁) antihistamines when they are unsuccessful as first- and second-line therapy. We performed a systematic review of the literature to identify studies that evaluated the efficacy of omalizumab for the treatment of chronic idiopathic urticaria, both in controlled and real-world settings, to assess its potential role as a preferred therapy. The PubMed, ScienceDirect, LILACS (Latin American and Caribbean Health Sciences Literature), and Google Scholar databases were searched between January 1, 2000 and November 21, 2016. The search was limited to articles published in peer-reviewed journals in the English language, and 29 studies were included in this review. Omalizumab 300 mg administered every 4 weeks appears to be the most effective and safe dosage, with a rapid response time, for the treatment of chronic idiopathic urticaria, with few minor adverse effects, and appears to be safe in the offspring of pregnant patients who received the drug. However, as published studies of omalizumab are sparse, future studies are warranted. When findings are confirmed in larger studies, due to its efficacy, safety, and increased benefit/cost ratio, omalizumab could become the preferred method of treatment for chronic idiopathic urticaria in patients unresponsive to H₁ antihistamines.

Introduction

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), manifests as itchy wheals and/or angioedema, arising without an evident external trigger and persisting for at least 6 weeks (if less than 6 weeks, it is termed acute urticaria), and typically for about 10 months.^{1,2}

CIU is typically considered to be caused by autoantibodies,³ but sometimes the cause is unknown, and features altered basophil phenotypes, whereas induced urticarias are mainly related to external triggers and include solar urticaria, heat urticaria, cold urticaria, contact

urticaria, aquagenic urticaria, delayed pressure urticaria, vibratory urticaria, and cholinergic urticaria. In CIU, histamine, together with blood basophils, cutaneous mast cells, and immunoglobulin E (IgE), is thought to play a key role as a fundamental mediator; therefore, most treatments concerning this condition rely on antihistamine products. Indeed, typical therapies for CIU are histamine receptor type 1 (H₁) antihistamines.⁴ Such compounds competitively inhibit H₁ receptors, with the corresponding effects of increased vasodilation and capillary permeability. H₁ antihistamines that penetrate into the brain typically elicit drowsiness by inhibiting the stimulant effect of histamine. In fact, they are not able to inhibit antigen-antibody reactions, nor histamine release, but they inhibit H₁ effects. In addition to this antihistaminic effect, they are capable of having parallel pharmacologic properties, for example, antimuscarinic and adrenolytic effects, which must be considered.

Typically, H₁ antihistamines are categorized into two classes: the older first-generation agents, which are commonly sedating, and the more recent (modern) second-generation agents, which have slight or no sedating effects, as it is believed that they do not cross the blood-brain barrier. In some cases, however, high doses of H₁ antihistamines provide unsatisfying results, with patients still experiencing symptoms despite receiving treatment.⁵ In such cases, a support therapy is often used, mainly consisting of leukotriene receptor antagonists or cyclosporine,^{4,6} or oral corticosteroids, which are potentially harmful for long-term use. More specifically, the recommended treatment algorithm for urticaria consists of three major steps.² As first-line treatment, second-generation antihistamines are employed.² If symptoms persist after 2 weeks of treatment, second-line treatment consists of an increase in the dosage of these antihistamines up to 4-fold.² After 1-4 further weeks, if symptoms persist, third-line treatment should be adopted by adding omalizumab, cyclosporine, or montelukast to second-line treatment, with a short course of corticosteroids (maximum 10 days) in cases of exacerbations.²

Thus, omalizumab has been proposed as a possible effective treatment of chronic urticaria,⁷ at least as a third-line solution.⁸ Omalizumab is a humanized IgG monoclonal antibody recognizing the Fc portion of IgE and is normally employed for the treatment of allergic asthma not responsive to standard therapies⁹ or atopic dermatitis (although this is not an approved use of the agent).¹⁰ Omalizumab is thought to reduce IgE- and FCεRI-mediated mast cell and basophil activation,^{11,12} with a similar outcome on mast cells and basophils according to recent evidence.¹³ However, being an extremely innovative treatment for this particular pathology, clinical trials with the agent are few. Therefore, a systematic review evaluating the use of omalizumab in the

treatment of chronic urticaria could be extremely useful to assess its efficacy, its eventual resistance to the therapy within any particular cohort, and its potential role as a preferred future treatment. To provide comprehensive and in-depth insight of the current literature, this systematic review not only included clinical trials, which are normally performed in a very structured environment, but also observational studies and case reports, often involving a smaller number of subjects when compared to clinical trials, but more closely reflecting the ordinary situations in which the drugs will be employed, thus possibly reinforcing their clinical and pharmacologic value.

Methods

A systematic literature review (January 1, 2000–November 21, 2016) of the PubMed, Science Direct, LILACS (Latin American and Caribbean Health Sciences Literature), and Google Scholar databases was conducted according to PRISMA guidelines.¹⁴ The search strategy was as follows: ("anti-IgE antibodies"[Supplementary Concept] OR "anti-IgE antibodies"[All Fields] OR "anti ige"[All Fields]) OR (("omalizumab"[MeSH Terms] OR "omalizumab"[All Fields]) AND chronic[All Fields] AND idiopathic[All Fields] AND ("urticaria"[MeSH Terms] OR "urticaria"[All Fields])). Methods for study selection and inclusion criteria were documented in the PROSPERO (an international prospective register of systematic reviews) protocol CRD42016035512. The search was limited to articles published in peer-reviewed journals in the English language. The identified studies were sorted by relevance, and the most significant studies associating anti-IgE antibodies and CIU in humans were selected. We first present the results from the literature review and then critically discuss the possible implications of using anti-IgE antibodies for the treatment of CIU in light of the most recent findings.

Results

The results of the systematic literature review are detailed in Figure 1, and a summary of the 29 included studies directly focusing on omalizumab and its use in the treatment of CIU during the period of investigation are displayed in Table 1.

Evidence from Observational studies

The first included study, published in 2008, was a retrospective case series performed in the United States.¹⁵ Twelve patients with chronic autoimmune urticaria (CAU) who experienced symptoms for at least 6 weeks despite antihistamine treatment were treated with placebo for 4 weeks and then switched to omalizumab at doses ≥ 0.016 mg/kg/IU ml⁻¹ IgE per month every 2-4 weeks for 16 weeks. Their overall quality of life, as assessed through use of the urticaria activity score (UAS), was significantly improved, with seven patients experiencing a complete remission and four patients having a partial remission; one patient did not respond. No adverse effects were seen in the cohort studied.

Four years later, a Turkish case series of 12 patients with CSU and two with idiopathic recurrent angioedema (IRA) was published.¹⁶ These patients did not benefit from the recommended first-, second-, and third-line treatments. Omalizumab was then administered at the recommended dosages according to the guidelines suggested for severe asthma treatment. UAS and quality of life (QoL) were evaluated after 1 and 6 months of therapy, displaying overall improvement in all patients. No adverse effects were seen during or after omalizumab treatment.

Further evidence of omalizumab efficacy was seen in two studies, the first in Spain¹⁷ and the second in France,¹⁸ both published in 2013. The Spanish study evaluated the effectiveness of omalizumab in 15 patients with CIU, 12 of whom responded within the first 3 months of treatment (3 with complete response, 9 with partial response).¹⁷ At month 6, 8 of 10 patients who continued omalizumab therapy had a complete response, with the two others having a partial response. On the other hand, the French study evaluated three patients with refractory chronic cold urticaria (CCU) and found the optimal dose and dosing interval to be a starting cycle of four subcutaneous injections of omalizumab 300 mg every 2 weeks, with subsequent injections given depending on the progression of the symptoms.¹⁸ The three patients studied all displayed remission of symptoms; however, in two of them, disease-related symptoms reappeared during a period of treatment interruption, suggesting that shorter therapy cycles should be restarted in both patients, which rapidly resulted in normalization of the symptoms.

Another retrospective clinical analysis was published in 2014. This German research aimed at evaluating the efficacy of omalizumab in a cohort of 51 patients with chronic urticaria (CU), of whom 20 had CIU alone, 21 had chronic inducible urticaria (CindU), and 10 experienced both CIU and CindU.¹⁹ Treatment started with omalizumab 150 (for patients included later in the study), 225, or 350 mg every 2-4 weeks, and doses were titrated up or down depending on their response to the treatment. Of the 30 patients with CIU (20 with CIU alone and 10 with CIU plus CindU), 25

(83%) experienced a complete remission of their symptoms, 3 (10%) showed significant improvement, and only 2 (7%) experienced no significant changes in their symptoms. The optimum interval between omalizumab doses was established to be 4 weeks for the majority of patients, in some cases extended to 6-8 weeks, and in only one patient was it decreased to 2 weeks due to the reappearance of symptoms. The starting dosage of 150 mg every 4 weeks seemed to be sufficient to improve symptoms, with only 2 of 15 patients requiring dose increases, whereas a dosage of 300 mg every 3-4 weeks was also proven to be useful in patients included earlier in the study. Only in one extreme case was a dosage of 450 mg every 4 weeks necessary to produce a complete remission of symptoms.

Of the patients with CindU, the majority (71%) displayed a similar response as the patients with CIU. Also, regarding omalizumab dosages, for a large subgroup, a dosage of 150 mg every 4 weeks was enough to produce a positive outcome, whereas in only two patients, the optimum dose was up to 450 mg. The relapse time (before reappearance of urticaria symptoms) varied between 2 and 8 weeks for all but 6 patients. Overall, 89% of patients showed a significant improvement or complete response to omalizumab before their second visit to the clinic, normally between 2 and 4 weeks after beginning therapy. For all 51 patients, omalizumab was proven to be safe, and its efficacy was not correlated with baseline IgE levels.

Another interesting prospective study was conducted in Canada and involved two clinical centers (Toronto and Quebec City).²⁰ The aim of this research was to evaluate the efficacy of a treatment with omalizumab 150 mg/month in patients with severe, difficult-to-treat, CU. Sixty-eight patients were included in this study, of whom 61 had CIU, 6 had cold urticaria (CoU), and 1 had urticarial vasculitis (UV), and they were followed for up to 25 months. The mean 7-day urticaria activity score (UAS-7) decreased in the Toronto cohort from 32.2 at baseline to 5.7 after omalizumab treatment, with 79% of patients experiencing a complete remission of symptoms and 18% showing improvement. The average maintenance dosing intervals were between 1 and 3 months. On the other hand, in the Quebec City group, the mean UAS-7 decreased from 24.4 to 2.2 after the treatment, with a complete remission of symptoms in all the patients enrolled in this center. As in the previous study,¹⁹ the 150-mg/month dose of omalizumab was proven to be completely safe in all patients treated.

A retrospective chart review was performed that included 48 patients (of whom 43 had CIU, 2 had UV, and 3 had urticarial bullous pemphigoid); for the patients with CIU, the mean age was 43.2 years and 79.1% were female.²¹ Omalizumab was effective within 3 months for 90.2% of

patients, with higher response rates were achieved by treating patients with omalizumab 300 mg every 2 weeks instead of every 4 weeks.

A similar approach was undertaken in a study by Giménez-Arnau and colleagues that retrospectively evaluated 38 patients with CIU, with all receiving omalizumab 300 mg every 4 weeks.²² The treatment produced a 68.4% complete response rate (UAS-7 = 0), with patients then having the option to stop treatment with corticosteroids, cyclosporine, and antileukotrienes. Only 39.5% of patients remained on antihistamines. Furthermore, a 96% and 65% decrease in emergency department and primary health care visits, respectively, was seen, with an overall reduction in the direct costs associated with the disease. No drug-related adverse events were reported.

Similarly, Ghazanfar and colleagues reported overall effectiveness of omalizumab in a retrospective review of 154 patients (110 females, 44 males), 137 of whom had CIU (mean age 35.9 years at onset and 39.7 years at treatment) and 17 had CindU.²³ An initial dose of omalizumab 150 mg every 2 weeks was administered in 45% of patients, whereas 300 mg every 4 weeks was administered in 55% of patients. Among the patients starting on 150 mg every 2 weeks, 83% stayed on the same dose and dosing interval throughout the observation period, 6% were changed to 150 mg every 4 weeks, and 11% were changed to 300 mg every 2-4 weeks. On the other hand, among the patients started on 300 mg every 4 weeks, 87% stayed on the same dose and dosing interval throughout the observation period, 6% were changed to 150 mg every 2-4 weeks or 300 mg every 6 weeks, and 7% were changed to 300 mg every 2-3 weeks. Sixty-seven percent of patients with CIU responded completely or almost completely to the treatment, 22% responded partially, and 10% had no or limited response to treatment. Fourteen percent of patients experienced adverse effects during treatment, including suspected allergic reactions, gastrointestinal symptoms, injection-site reactions, worsening urticaria, headache, dizziness, arthritis, and fatigue. All adverse effects were reversible. One year after initiation of omalizumab, 56% of the patients with CIU were still on continuous treatment, whereas 44% had discontinued treatment due to any cause, including symptomatic remission, lack of effect, nonadherence to scheduled ambulatory visits, adverse effects, or pregnancy.

A retrospective, observational study was conducted in Brazil, published in 2016, that involved 47 patients with CIU (7 males, 40 females), aged 16-74 (mean 38.9) years, who were unresponsive to modern antihistamines.²⁴ Omalizumab 150 or 300 mg was administered

subcutaneously every 4 weeks, with the dose depending on the availability of the drug in the reference clinical center. Patients were treated an average 11.4 times (range 2-87), and evaluation of their quality of life and urticarial symptoms was performed. Among the patients initially treated with the higher dose (300 mg), 84.6% experienced a complete remission of symptoms, whereas complete remission occurred in only 60% of patients starting treatment with the 150-mg dose. Overall, omalizumab treatment was noted to be effective, and no related adverse events were seen.

Finally, in a retrospective analysis conducted by Gericke and colleagues, omalizumab 300 mg every 4 weeks was administered in a cohort of 64 patients with CIU who were previously unsuccessfully treated with high doses of H₁ antihistamines in order to check for its overall efficacy and response time.²⁵ Among those enrolled, basophil histamine release assay (BHRA)-positive patients displayed a slower response time (median of 29 days), whereas subjects with a negative BHRA experienced a faster positive treatment outcome (just after a median of 2 days).

Evidence from Randomized Studies

The first reported use of omalizumab for the treatment of CU dates back to 2006, when a 12-year-old child suffering from cold-induced urticaria (CoiU) was treated with omalizumab for allergic asthma.⁴⁴ The agent improved his urticarial condition, and his symptoms were completely resolved within 5 months of beginning treatment. Since then, several studies have been published to date, and in particular during more recent years, with advances in the effectiveness of omalizumab for CIU becoming more convincing throughout the years. In particular, a wide contribution to the literature in this field was provided by phase II/III studies.

Saini and colleagues evaluated 90 patients with CIU in a phase II, prospective, double-blind, placebo-controlled, dose-ranging study published in 2011. Patients were randomly assigned in a 1:1:1:1 ratio to receive a single subcutaneous dose of 75, 300, or 600 mg of omalizumab or placebo added to a stable dose of H₁ antihistamine.²⁶ The primary efficacy outcome was the change in UAS-7 from baseline to week 4, whereas to assess safety of the treatment, an additional 12 weeks of follow-up was included to monitor for eventual adverse effects. Based on that experimental setting, it was found that a fixed dose of 300 or 600 mg of omalizumab provided rapid and effective treatment of CIU in this cohort.

The ASTERIA I²⁹ and ASTERIA II²⁷ trials evaluated the efficacy and safety of add-on omalizumab 75, 150, or 300 mg versus add-on placebo in patients with CIU who remained symptomatic despite treatment with approved doses of H₁ antihistamines. These studies were similar in design, except that the double-blind treatment period was twice as long in ASTERIA I (24 weeks) than in ASTERIA II (12 weeks). ASTERIA I was conducted to evaluate the potential effects of treatment over a longer duration, in part because the symptoms of CIU wax and wane over time. In this study, the introduction of an additional H₁ antihistamine was allowed after week 12, with the aim of reducing patient dropout over the longer treatment period.

The GLACIAL study, which was more similar to real-life conditions than the classic randomized study, was otherwise conducted to evaluate the safety and efficacy of omalizumab 300 mg versus placebo in patients with CIU who remained symptomatic despite receiving up to four times the approved dosage of H₁ antihistamines and either an H₂ antihistamine or leukotriene receptor antagonist, or all three in combination.²⁸ The primary objective of GLACIAL was to assess the safety of omalizumab in patients who were receiving different add-on therapies for CIU, although efficacy end points from ASTERIA I and II were also evaluated as secondary end points.

Overall, the ASTERIA I, ASTERIA II, and GLACIAL studies showed a dose-dependent response pattern to omalizumab treatment of CIU, with the use of the 300-mg dose of omalizumab resulting in the highest proportion of patients with complete response (UAS7 = 0) or well-controlled urticaria (UAS7 ≤ 6). Half of the patients treated with omalizumab 300 mg had well-controlled symptoms after 2 injections (median time to response of 6 weeks). The benefits of omalizumab treatment in patients with CIU have been evident up to week 24.⁴⁵

The overall safety and efficacy of omalizumab relative to placebo was also evaluated in patients with moderate-to-severe CIU symptoms and angioedema unresponsive to high doses of antihistamine treatment in the X-ACT study.³⁰ Patients receiving omalizumab had a positive outcome at week 28 and a longer time to angioedema relapse compared with placebo-treated patients.

Databases from the ASTERIA I, ASTERIA II, and GLACIAL trials were employed in two studies published in 2016, one of which dealt with the assessment of omalizumab efficacy in reducing angioedema in patients previously treated with either H₁ antihistamines at licensed doses (ASTERIA I and II) or at up to 4 times the approved dose plus H₂ antihistamines and/or a leukotriene receptor antagonist (GLACIAL).³² This study evidenced that low-intensity treatment composed of omalizumab 300 mg is normally efficacious in reducing patient-reported

angioedema. The second study analyzed the adverse effect of sleep disturbances possibly associated with use of omalizumab.³¹ In the 975 patients included in this study, a reduction in sleep problems was noted for omalizumab-treated patients relative to placebo-treated patients, particularly evident when omalizumab 300 mg was administered, emerging within the first 4 weeks of therapy.

Evidence from Case Reports

Further evidence trending in the same direction was noted in a few case reports in which patients with particularly difficult cases were included.³⁸⁻⁴³ Although it is unlikely that this evidence increased the statistical significance of the overall findings in the literature, it enlarged the spectrum of the clinical cases for which omalizumab treatment was demonstrated as effective.

In one of the first case reports published to date, Dreyfus assessed the symptoms of a 22-year-old female with CIU and comorbid asthma and thyroid autoimmunity while receiving multiple steroid-sparing therapies, without displaying exacerbations of urticaria or anaphylaxis.³³ In this patient, omalizumab brought a rapid reduction and consequent elimination of oral steroid requirement. After 6 months of therapy, serum factors capable of triggering mast cell and basophil release, as well as levels of thyroid autoantibodies, had increased. At that time, thyrotropin levels were abnormally elevated. Steroid-dependent urticaria and asthma returned after therapy was stopped for 3 months, despite being absent when treated with omalizumab, during which normalized thyroid function was also seen.

A particularly difficult case was reported by Iemoli and colleagues in Italy, involving a 57-year-old woman with CU/angioedema syndrome, previously unsuccessfully treated with corticosteroids, antihistamines, and antileukotrienes.³⁴ In this case report, omalizumab 300 mg was administered subcutaneously every 2 weeks for a 6-month period. After the first injection, symptoms disappeared in a few days, with reappearance after 1 month of treatment interruption. Therefore, omalizumab therapy was restarted and was rapidly effective after the first injection. A similar outcome was noted in a 35-year-old woman presenting with the same comorbidities who was treated with similar omalizumab dosing and had similar rapid improvement.³⁷

Particularly tricky was also the case reported by Saavedra and Sur in the United States.³⁶ A 51-year-old woman with CU and a history of asthma, allergic rhinitis, and atopic dermatitis without previous benefits from montelukast was treated with omalizumab 300 mg every 2 weeks and, subsequently, every 3 weeks, after 28 weeks of therapy. Significant improvements associated

with the therapy were noticed, without any particular adverse effects except for three episodes of hives that were easily managed. Similarly, a 15-year-old female with an adverse reaction to aspirin as well as chronic rhinosinusitis, severe asthma, and CIU worsened by nonsteroidal antiinflammatory drug administration was treated with omalizumab 300 mg every 4 weeks for 6 months.⁴³ A decrease in peripheral eosinophil count was noted at her monthly visit, with an improvement in spirometry parameters such as fractional exhaled nitric oxide (FEV1) and forced expiratory volume (FeNO) in the first second from baseline. Furthermore, cutaneous symptoms were also improved, despite displaying a relapse of such symptoms just after 1 month of discontinuation of therapy, requiring systemic corticosteroid therapy to improve this condition.

A particularly severe form of CIU was treated with omalizumab in two Danish women, both initially administered omalizumab 300 mg subcutaneously every fourth week.³⁵ However, one of the two patients experienced abdominal adverse effects, and her dose was decreased to 150 mg every fourth week. This patient had a partial resolution of symptoms, with few adverse effects possibly due to a longer dosing interval of 6 weeks due to her unavailability at the 4-week visit.

SU was also studied in two case reports by Arasi and colleagues³⁸ and Zimmer et al.⁴¹ The first report described a 16-year-old, Italian, Caucasian girl with an 18-month history of SU unresponsive to several attempts with conventional therapies.³⁸ From the very beginning of treatment, the patient's quality of life was seriously compromised due to SU, with slight allergic rhinitis to grass and *Alternaria* as other coexisting conditions, without displaying any of the common causes of urticaria and photodermatosis. She experienced SU unresponsiveness to three H₁ antihistamines at standard dosages (cetirizine 10 mg/day, desloratadine 5 mg/day, and hydroxyzine 25 mg/day) as well as unresponsiveness to an H₁ antihistamine at a double dose (cetirizine 20 mg/day), an H₂ antihistamine at a standard dose (ranitidine 150 mg/day), and an antileukotriene (montelukast 10 mg), always taken with high-grade sun block. Furthermore, short treatments of oral prednisone (25 mg daily over 5 days) were also ineffective, with SU reappearing during sunlight exposure. At this point, omalizumab treatment was started, based on her initial serum IgE level and body weight, with a 375-mg dose administered subcutaneously every 2 weeks. Rapid improvement of symptoms was seen after the first omalizumab administration and during maintenance, as well as after dose reduction, prescribed once she completed the typical 6-month treatment.

Zimmer and colleagues reported the case of a 71-year-old woman with SU who had UVA-induced urticaria for 11 years and developed CoU 6 years later.⁴¹ She developed wheals and pruritus (Urticaria Control Test score of 3) in response to cold air and/or UV radiation, with a significant decrease in life quality (score of 29 on the Chronic Urticaria Quality of Life Questionnaire [Cu-Q2oL]). Her resistance to different antihistamines at up to 4 times the licensed doses resulted in initiation of treatment with omalizumab, with a 300-mg dose administered subcutaneously every 4 weeks. Four weeks after the first dose of omalizumab, the patient displayed an improvement in life quality (Cu-Q2oL score of 18) and in urticarial symptoms (Urticaria Control Test score of 11) without any response to cold provocation testing until 4°C. UVA provocation testing showed erythema and hives but without compromising her overall life quality. Therefore, antihistamines were discontinued after 4 months of omalizumab therapy. Five months later, she had a relapse of urticarial symptoms and burden of disease, once more controlled within 2 further months of omalizumab therapy.

Two cases reported by Ghazanfar and Thomsen^{39, 40} addressed to two very different categories of patient. The first case report described the positive use of omalizumab in a 68-year-old man who developed severe skin rashes typical of UV.³⁹ The initial prednisolone dosage of 37.5 mg once daily improved his symptoms, with an overall positive outcome after the washout (25 mg daily for three days, 12.5 mg daily for one week), but his symptoms reappeared after 3 months. The treatment with dapsone 50 mg twice daily failed to produce any improvement; therefore, subcutaneous omalizumab 300 mg was administered once every 4 weeks. A complete remission of the UV was observed after one month and, at the time of the publication, the patient did not display apparent adverse effects.

The second report described a 32-year-old woman with severe CIU with angioedema, atopic dermatitis, and asthma.⁴⁰ The patient experienced symptoms of urticaria on a daily basis, dramatically affecting her sleep quality. During the treatment with subcutaneous omalizumab 150 mg every 2 weeks (after unsuccessful treatments with cetirizine 10 mg up to 3 times daily, azathioprine 100 mg daily, prednisolone for 4 days, and azathioprine 125 mg and adalimumab 40 mg once every 2 weeks), the patient became pregnant, deciding to maintain the omalizumab treatment. Thirty-eight months after birth, the child did not experience any developmental abnormality. Furthermore, after changing the dose to 300 mg once monthly, due to symptoms of remission, a second pregnancy occurred, and the baby did not experience any abnormality 5 months after birth.

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It is worth noting, however, that the use of omalizumab during pregnancy is still debated and not recommended by any accepted national or international guidelines; therefore, data regarding this debate should be carefully taken into account. Finally, omalizumab appeared to be safe even in the treatment of children or adolescents,^{35, 36, 38} in two different contexts— SU in the first case³⁸ and CIU with concomitant other comorbidities in the second and third cases^{35, 36}— however, studies in larger cohorts are required before any reliable conclusions can be drawn.

Discussion

Omalizumab is a recombinant humanized monoclonal antibody to IgE, built through the insertion of a mouse complementarity-determining region of monoclonal anti-IgE onto the consensus sequence of human IgG1.⁴⁶ In particular, this antibody is able to bind IgE at the same epitope (CH3) as the α -chain of Fc ϵ RI, decreasing the expression of IgE receptors with high affinity, preventing the bond between IgE and its receptor,⁴⁷ and, therefore, not inducing the release of histamine from the IgE bound on the surface of basophils and mast cells. The bond between omalizumab and IgE decreases previously free IgE levels that, not being free to bind Fc ϵ RI anymore, cause a decreased expression of high-affinity IgE receptors on mast cells and basophils.⁴⁸ Experimental results on atopic cohorts demonstrated a decrease of free IgE and FC ϵ RI levels in a short time period (only 3 days) to 1-4% of pretreatment levels,⁴⁹ linked to the evidence that a decrease in the number of receptors decreases the release of mediators and subsequent allergic inflammation.^{50, 51} Although most studies evaluating omalizumab were conducted in atopic populations, most patients with CIU are not considered atopic; therefore, the mechanisms of action of omalizumab in the treatment of CIU could be quite different.

Overall, the results from the studies analyzed reported the overall safety of omalizumab, which could have represented one of the most likely concerns of using this treatment approach. Safety was demonstrated both for patients treated with omalizumab and for their offspring, as shown in the interesting case report by Ghazanfar and Thomsen,⁴⁰ even in the case where the antibody was administered during pregnancy. Only in a few particularly difficult cases, adverse effects were reported that were minor compared with the benefits of this treatment. Data concerning the use of omalizumab during pregnancy, however, should be taken into consideration carefully, as highlighted in the EXPECT study,⁵² which reported the absence of an increased prevalence of major birth anomalies or patterns of major birth anomalies, while recognizing the limitation of the small sample size. Therefore, although omalizumab may be safe to use in

pregnant patients when necessary, it is worth emphasizing the lack of a recommendation for use in this population. Efficacy and overall safety were also observed among children,⁵³ whose pathological mechanisms seem to be similar to those of adults, according to Ulrich.⁵⁴

Another important finding was the significant clinical response to omalizumab treatment in patients with CU independent of disease severity or IgE levels at baseline, as also happens in patients with CAU.⁵⁵ Indeed, in large cohorts (51 patients in one study, 68 subjects into two different clinical centers in another study, 43 patients in a retrospective chart evaluation, and 47 subjects in a retrospective observational study), with several patients who had serious symptoms for CU and were probably not able to remain free of medication for any period of time, omalizumab was clearly effective in reducing or mostly resolving the common symptoms of the disease,^{19, 20, 22-24, 30} even in the case of unresponsiveness to H₁ antihistamines⁵⁶ and second- and other third-line therapies managed according to the international guidelines for CU.² However, it is worth noting that omalizumab therapy is a symptomatic treatment, and symptoms almost invariably recur when therapy is stopped. This should be kept in mind when using a symptomatic treatment. Despite that, data from specific subgroups are lacking, as are adequate sample sizes (e.g., for patients with CindU); therefore, further large-scale efficacy evidence of omalizumab within various populations is needed.

Positive responses to omalizumab treatment were found in both placebo-controlled trials, reflecting efficacy in a very structured, controlled environment,²⁷⁻³⁰ and in retrospective and prospective observational clinical studies, more strongly reflecting real-life situations for the patients treated, but in some cases resulting in heterogeneity of the study population or other biases that could have affected a small percentage of the positive outcomes.^{19, 20, 23, 24} Overall, treatment with omalizumab was found to be particularly effective with a dosage of 300 mg administered subcutaneously every 4 weeks, as most of the studies published to date employed this dose and dosing interval combination, demonstrating efficacy and overall safety in most cases.

Omalizumab and CU: Hypotheses on Mechanisms of Action

Concerning the mechanisms of action of omalizumab in patients with CU, as mentioned above, CU is quite different from the other conditions including, for example, allergic asthma. In fact, IgE involvement is much more of a central concern in asthma, where IgE levels should be kept under control through continuous administration of anti-IgE products. On the other hand, in CU, most recommendations suggest the administration of anti-IgE antibodies for 6 months within each

cycle, with an 8-week interruption between two consecutive cycles due to a more important role for the mast cells and a secondary involvement of IgE. This may occur because of the higher IgE levels present in asthmatic patients and allergic inflammation in the bronchi,⁵⁷ a much more persistent phenomenon compared with the skin effects occurring in patients with CIU.

In most of the studies analyzed, baseline conditions of the patients did not correlate with their final outcomes after omalizumab treatment. Therefore, unlike asthma, where dosing is based on body weight and IgE levels, IgE levels do not seem particularly relevant to the efficacy of the treatment, leading to the hypothesis that omalizumab may have nonspecific activity in the stabilization of mast cells. However, the responsiveness of the skin to histamine often appears unaltered, like the dermal response to codeine,¹⁹ somehow disputing this hypothesis. It is worth noting, however, that IgE level is more centrally involved in asthma than in CIU; therefore, IgE level is related to omalizumab efficacy in a distinctly different manner for each of these conditions.

One of the most likely mechanisms of action of omalizumab in CIU is through the sequestration of monomeric IgE to reduce its priming effect on mast cells in the case that IgE is involved in the pathogenesis of urticaria.⁵⁸ In subjects with IgG autoantibodies against IgE or FCεRI, omalizumab could cause the depletion of mast cell-bound IgE followed by the downregulation of FCεRI on mast cells and basophils, decreasing their hyperexcitability.⁵⁸ Then, when autoallergens are in the presence of IgE, omalizumab could inhibit the bond between IgE and FCεRI, downregulating FCεRI and causing an accumulation of immune complexes of omalizumab-IgE that sequester endogenous autoantigens normally reacting with IgE.⁵⁹

Overall, the intervention of omalizumab causes an increase in the threshold for activation of mast cells to undergo degranulation, thus decreasing mast cell sensitivity and increasing their stability, consequently diminishing the manifestation of urticarial symptoms (Figure 2). When this antibody is used for treatment, it also decreases the release of inflammatory cytokines and mediators from basophils in the vasculature, reducing skin inflammatory processes. This overall effect is important especially in the first phase of the treatment period, with downregulation of FCεRI on basophils being faster than that on mast cells.

Economic Considerations

Use of omalizumab is quite costly compared with other treatments commonly employed for CIU. Despite this, according to recent evidence, this product—innovative for this particular use—has been demonstrated to reduce direct costs.^{22, 60, 61} Indeed, the leading contributor to the overall expense of omalizumab treatment is the cost of the drug itself, as outpatient clinic and emergency department costs have been lower due to the effectiveness of the treatment.⁶⁰ Therefore, use of omalizumab in patients with CIU appears to be justified due to its increased benefit/cost ratio.⁶⁰

Conclusion

Omalizumab could become the preferred treatment for CIU as well as difficult cases of similar conditions in patients unresponsive to H₁ antihistamines, as it has demonstrated efficacy and safety in adults and children, as well as the offspring of pregnant patients.^{8, 62} However, further data from studies of larger cohorts and subgroups of specific populations would be highly desirable to confirm the current evidence, both in real-life settings such as observational studies and case reports, and controlled settings such as randomized clinical trials. Also, although the evidence from the existing literature suggests a dosage of omalizumab 300 mg every 4 weeks as a preferred therapy for CIU in most cases, standardized protocols related to dosing as well as monitoring of long-term adverse effects require future research.

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Table 1. Summary of Studies of Omalizumab for the Treatment of Chronic Idiopathic Urticaria

Year of Publication and Country	No. of Patients	Design, Population, Treatments, and Outcome Measures	Results
Observational studies			
Kaplan et al. (2008) United States ¹⁵	12 (12/0) ^a	Retrospective case series; 12 patients with CAU with persistent symptoms for at least 6 weeks despite antihistamines, treated with placebo for 4 weeks followed by omalizumab (≥ 0.016 mg/kg/IU ml ⁻¹ IgE per month) every 2 or 4 weeks for 16 weeks; UAS and quality of life assessed	UAS decreased from baseline to after omalizumab treatment; 7 patients had complete symptom resolution, 4 patients had a mean decrease in UAS but urticaria persisted, and 1 patient did not respond; rescue medication use was reduced, and quality of life improved; no adverse effects were reported
Büyüköztürk et al. (2012)	14 (12/2) ^a	Case series; 12 patients with CSU and 2 with IRA treated with omalizumab	QoL scores and UAS significantly improved in all patients; no adverse

Turkey ¹⁶		after not having benefited from the recommended first-, second-, and third-line treatments; UAS and QoL scores measured at baseline and at the end of the first and sixth month of therapy; dosage and intervals of omalizumab therapy were determined according to the guidelines suggested for severe asthma treatment	effects reported
Armengot-Carbo et al. (2013) Spain ¹⁷	15 (15/0) ^a	Retrospective case series of 15 patients with CIU treated with omalizumab	After 3 months of treatment, 12 patients responded (9 had partial response, 3 had complete response); at 6 months, 8/10 patients who continued omalizumab had complete response, 2/10 had partial response
Le Moing et al. (2013) France ¹⁸	3 (3/0) ^a	Case series; 3 patients (3 females, aged 21, 42, and 66 yrs) with refractory CCU previously treated unsuccessfully for at least 6 weeks; treatment with 4 subcutaneous injections of omalizumab 300 mg every 2 weeks, with subsequent injections given depending on the symptoms	Patient 1: after 4 injections, symptoms remained controlled for 16 months without further treatment Patient 2: relapsed 4 months after the fourth injection; after fifth 300-mg omalizumab dose administered, had rapid remission maintained for 5 months; mild relapse rapidly controlled by a sixth 300-mg omalizumab dose Patient 3: complete remission after 4 injections; after 1 month of treatment disruption, the urticaria reappeared; after fifth 300-mg omalizumab dose, complete remission maintained for 2 months
Metz et al. (2014) Germany ¹⁹	51 (51/0) ^a	Retrospective clinical analysis of omalizumab efficacy in 51 patients with CU: 20 with CIU alone, 21 with CindU, and 10 with both; responder rates, optimal dosage, response to up- or down-dosing, time to relief of symptoms, rates of return, time of relapse after omalizumab administration, and safety were evaluated	Complete remission in 83% (25/30) of CIU and 71% of CindU patients. Starting with omalizumab 150 mg every 4 weeks, only 2/15 CIU and 7/17 CindU patients required upward titration of doses for complete remission. In CSU patients, 57% had complete responses within week one, all on the first day. Relapses occurred 2–8 weeks later in all but 6 patients (<4 months). Omalizumab was safe. Efficacy was not correlated with baseline IgE levels.
Sussman et al. (2014) Canada (Toronto and Quebec City) ²⁰	68 (61/7) ^a	Prospective study to evaluate omalizumab 150 mg/month in patients with severe, difficult-to-treat, CU. 68 patients included: 61 with CSU, 6 with CoU, 1 with UV. Patients were followed for up to 25 months.	In the Toronto group, mean UAS-7 decreased from 32.2 at baseline to 5.7 after the last omalizumab treatment; 79% had complete remission during therapy (UAS-7 = 0), 18% had improvement without complete remission.

			In the Quebec City group, mean UAS-7 decreased from 24.4 to 2.2, and quantitative medication score decreased from 13.3 to 3.0, with 100% of patients experiencing complete remission. All 6 patients with CoU became symptom free, with a significant decrease in cold stimulation tolerance test. Omalizumab was found to be completely safe in all patients.
Clark et al. (2016) USA ²¹	48 (43/5) ^a	Retrospective chart review of 48 patients (43 CIU, 2 UV, 3 urticarial bullous pemphigoid). Mean age (for CIU) 43.2 years, 79.1% female	2/43 patients lost to follow-up; 90.2% (37/41) responded to omalizumab within 3 months. Higher response rates achieved by treating CIU patients with omalizumab 300 mg every 2 weeks instead of every 4 weeks
Giménez-Arnau et al. (2016) Spain ²²	38 (38/0) ^a	Retrospective analysis of 38 patients with CIU receiving omalizumab 300 mg every 4 weeks	68.4% of patients had complete response (UAS-7 = 0). All the patients stopped treatment with corticosteroids, cyclosporine, and antileukotrienes; only 39.5% of patients remained on antihistamines. 96% and 65% decrease in emergency department and primary health care visits, respectively; overall reduction in direct costs. No adverse events reported.
Ghazanfar et al. (2016) Denmark ²³	154 (137/17) ^a	Retrospective review of 154 patients: 137 with CIU, 17 with CindU; 110 females, 44 males. Initial dose of omalizumab 150 mg every 2 weeks in 45% of patients and 300 mg every 4 weeks in 55% of patients	Of the patients started on omalizumab 150 mg every 2 weeks, 83% stayed on the same dose and dosing interval throughout the observation period, 6% were changed to 150 mg every 4 weeks, and 11% were changed to 300 mg every 2–4 weeks. Conversely, of the patients who started on 300 mg every 4 weeks, 87% stayed on the same dose and dosing interval, 6% were changed to 150 mg every 2–4 weeks or 300 mg every 6 weeks, and 7% were changed to 300 mg at intervals every 2–3 weeks. One year after initiation of omalizumab, 56% of the patients with CIU were still on continuous treatment, and 44% had discontinued treatment
Ensina et al. (2016) Brazil ²⁴	47 (47/0) ^a	Retrospective, observational study of 47 patients with CIU (7 males, 40 females), aged 16–74 (mean 38.9) years, unresponsive to modern	84.6% of patients initially treated with omalizumab 300 mg had complete resolution of symptoms. 60% of patients initially treated with

		antihistamines, treated with omalizumab 150 or 300 mg subcutaneously every 4 weeks. Quality of life and symptoms evaluated.	omalizumab 150 mg had complete resolution of symptoms. Four patients dropped out (1 for lack of response, 1 for an abortion not related to the study drug, 2 due to limited access to drugs).
Gericke et al. (2016) ²⁵ Germany	64 (64/0) ^a	Retrospective analysis of 64 CIU patients (46 females, median age 47 years) with symptoms not controlled with high doses of H ₁ antihistamines, treated with omalizumab 300 mg every 4 weeks. BHRA and ASST used to test the response speed.	BHRA-positive patients were slow responders (median 29 days), BHRA-negative patients had a quick response (2 days). ASST somehow correlated with BHRA.
Randomized studies			
Saini et al. (2011) Germany and United States ^{27,26}	90 (69/21) ^b	Phase II, prospective, double-blind, placebo-controlled, dose-ranging study. Patients with CIU were randomized 1:1:1:1 to receive a single subcutaneous dose of 75, 300, or 600 mg of omalizumab, or placebo, added to a stable dose of H ₁ antihistamine. Primary efficacy outcome was change in UAS-7 from baseline to week 4. Patients were followed for an additional 12 weeks to monitor safety.	A fixed dose of 300 or 600 mg of omalizumab provides rapid and effective treatment of CIU in patients who are symptomatic despite treatment with H ₁ antihistamines.
Maurer et al. (2013) Various countries (ASTERIA II) ^{29,27}	323 (244/79) ^b	Phase III, multicenter, randomized, double-blind, placebo-controlled study of patients with moderate-to-severe CIU who remained symptomatic despite H ₁ antihistamine therapy. 323 patients were randomly assigned to receive three subcutaneous injections, 4 weeks apart, of omalizumab 75, 150, or 300 mg, or placebo, followed by a 16-week observation period. Outcomes were assessed by the change from baseline in a weekly ISS.	Omalizumab diminished clinical symptoms and signs of CIU. Adverse effects were few; however, they roughly correlated with omalizumab dose.
Kaplan et al. (2013) Various countries (GLACIAL) ^{29,28}	336 (252/84) ^b	phase III, multicenter, randomized, double-blind, placebo-controlled study of 336 patients with CIU treated with 6 subcutaneous injections at 4-week intervals of either 300 mg of omalizumab or placebo, followed by a 16-week observation period; evaluation of the overall safety of omalizumab was compared with placebo. Efficacy (itch severity, hives, and UAS) was evaluated at weeks 12 and 24	Adverse events were similar between omalizumab and placebo recipients; safety profile consistent with omalizumab in patients with allergic asthma. Significant improvements were noted at week 12 and were sustained to week 24
Saini et al.	318	40-week, randomized, double-blind,	Mean weekly ISS was reduced in the

(2015) Various countries (ASTERIA I) ²⁸²⁹	(318/0) ^a (238/80) ^b	placebo-controlled study of 318 patients with CIU/CSU, aged 12–75 years old, treated with omalizumab 75, 150, or 300 mg, or placebo, every 4 weeks for 24 weeks, followed by 16 weeks of follow-up	omalizumab-treated cohorts. The omalizumab 300-mg group met all nine secondary end points.
Staubach et al. (2016) Germany (X-ACT) ³²³⁰	91 (44/47) ^b	Phase III, randomized, double-blind study of 91 CSU patients with angioedema and wheals, randomized (1:1) to omalizumab 300 mg or placebo every 4 weeks up to week 24. Efficacy was evaluated at week 28.	68 patients completed the 28-week treatment phase (35 in the omalizumab group, 33 in the placebo group). Omalizumab was superior to placebo in improving quality of life scores at week 28 ($p<0.001$). A 3-fold improvement in angioedema-burdened days/week was noted with omalizumab (0.3) vs placebo (1.1). Omalizumab significantly improved angioedema-specific QoL ($p<0.001$). The overall safety of omalizumab was demonstrated.
Gimenéz - Arnau et al. (2016) Various countries ³⁴³¹	975 (975/0) ^a	10-month, controlled study of omalizumab's effect on sleep quality in 975 patients enrolled in the placebo-controlled phase III ASTERIA I, ASTERIA II, and GLACIAL trials. Sleep was assessed by sleep-related questions included in an electronic diary, the Chronic Urticaria Quality of Life Questionnaire, and the Medical Outcomes Study Sleep Scale	Reduction in sleep problems was noted for the omalizumab-treated patients, especially with the 300-mg dose, within the first 4 weeks of therapy
Zazzali et al. (2016) Various countries ³³³²	975 (975/0) ^a	Enrolled patients with CIU who remained symptomatic after H ₁ antihistamines at either licensed doses (in ASTERIA I and ASTERIA II) or at up to 4 times the approved dose plus H ₂ antihistamines and/or a leukotriene receptor antagonist (GLACIAL) in placebo-controlled phase III trials. Omalizumab was administered at doses of 75, 150, or 300 mg in ASTERIA I and ASTERIA II, and 300 mg in GLACIAL, or placebo subcutaneously every 4 weeks for at least 12 weeks. The Urticaria Patient Daily Diary was completed by patients, and angioedema features were assessed	Low-intensity treatment with omalizumab 300 mg was efficacious in reducing patient-reported angioedema
Case reports			
Dreyfus (2008) United States ⁴⁴³³	1	22-year-old woman with asthma and CIU who experienced thyroid autoimmunity while receiving multiple steroid-sparing therapies without exacerbations of urticaria or	Omalizumab brought a rapid reduction and elimination of oral steroid requirement. After 6 months of therapy, serum factors capable of triggering mast cell and basophil

		anaphylaxis	release as well as levels of thyroid autoantibodies had increased. Thyrotropin levels were abnormally elevated. Steroid-dependent urticaria and asthma returned after therapy was stopped for 3 months. No symptoms were noted while taking omalizumab, and thyroid function normalized.
Iemoli et al. (2010) Italy ⁴²³⁴	1	57-year-old white woman with CU/angioedema syndrome previously unsuccessfully treated with corticosteroids, antihistamines, and antileukotrienes. Omalizumab 300 mg subcutaneously every 2 weeks was administered for 6 months.	Improvement in symptoms and complete resolution of the urticaria were noted a few days after the first injection. After 1 month of treatment interruption, the urticaria reappeared. Omalizumab therapy was restarted, with rapid improvement of symptoms noted after the first injection.
Vestergaard and Deleuran (2010) Denmark ⁴⁵³⁵	2	33-year-old and 57-year-old women with severe CIU not responding to standard therapies. Patient 1 received omalizumab 300 mg subcutaneously every 4 weeks based on body weight and serum IgE level. Patient 2 received omalizumab 300 mg every 4 weeks; the dose was decreased to 150 mg every 4 weeks due to abdominal adverse effects. Outcomes were assessed through DLQI and UAS-7.	Overall efficacy of the treatment: symptoms resolved in patient 1; patient 2 had abdominal adverse effects and CIU reappeared, possibly due to a delayed dosing interval of 6 weeks due to visit postponement
Saavedra and Sur (2011) United States ⁴⁴³⁶	1	51-year-old woman with CU and history of asthma, allergic rhinitis, and atopic dermatitis without previous benefits from montelukast. She received omalizumab 300 mg every 2 weeks, which was changed to every 3 weeks after 28 weeks of therapy	Significant improvements were noted. No hypersensitivity reactions were experienced during the treatment. Three episodes of hives were easily managed.
Sánchez-Machín et al. (2011) Spain ⁴³³⁷	1	35-year-old woman with an 8-year history of CIU and angioedema with poor response to treatment. Cyclosporine 100 mg every 12 hours did not resolve all the hives. Omalizumab 300 mg every 2 weeks was started.	Decrease in urticarial lesions was noted 2 days after starting therapy
Arasi et al. (2015) Italy ³⁸	1	16-year-old Caucasian girl with SU unresponsive to H ₁ and H ₂ antihistamines and short courses of oral prednisone (25 mg daily over 5 days). SU reappeared during sunlight exposure. Omalizumab 375 mg subcutaneously every 2 weeks was given. After 6 months, the dose was reduced to a single dose of 300 mg in	Response was prompt after the first administration of omalizumab, and improvement persisted with the maintenance doses. Clinical remission was noted at the 4th month of stoppage.

		the 7th month and 150 mg in the 8th and 9th months of treatment, the agent was then discontinued	
Ghazanfar and Thomsen (2015) Denmark ³⁵³⁹	1	68-year-old man with UV treated with two cycles of omalizumab 300 mg once every 4 weeks	Cycle 1: complete remission of UV after 1 month. Cycle 2: sustained remission, and no apparent adverse effects were noted
Ghazanfar and Thomsen (2015) Denmark ³⁶⁴⁰	1	32-year-old woman with severe CIU and angioedema, AD, and asthma. Two cycles of omalizumab were given during two consecutive pregnancies: omalizumab 150 mg every 2 weeks and omalizumab 300 mg once monthly	Cycles 1 and 2: CSU remission and no consequences in the patient's offspring. The overall safety and efficacy of omalizumab was demonstrated during pregnancy.
Zimmer et al. (2015) Germany ³⁷⁴¹	1	71-year-old woman with SU for 11 years who developed CoU 6 years later. Both were resistant to high doses of different antihistamines. Omalizumab 300 mg subcutaneously every 4 weeks was initiated (cycle 1), discontinued after 4 months, and restarted after 5 more months (cycle 2).	Cycle 1: omalizumab therapy did not result in complete symptom control but produced a high increase in quality of life after 4 weeks, followed by a burden of the disease 5 months after cycle 1 was stopped. Cycle 2: same outcome as cycle 1 within 2 months
Olszowiec-Chlebna et al. (2016) Poland ³⁹⁴²	1	15-year-old girl with CSU and concomitant idiopathic anaphylaxis. Omalizumab 300 mg once every 4 weeks was administered for 6 months.	Patient was asymptomatic during therapy and 3 months after the end of the therapy
Porcaro et al. (2016) Italy ⁴⁹⁴³	1	15-year-old girl with an adverse reaction to aspirin as well as chronic rhinosinusitis, severe asthma, and CIU worsened by nonsteroidal antiinflammatory drug administration. Omalizumab 300 mg was administered every 4 weeks for 6 months.	Overall improvement of cutaneous symptoms of aspirin-exacerbated respiratory disease

AD = atopic dermatitis; ASST = autologous serum skin test; BHRA = basophil histamine release assay; CAU = chronic autoimmune urticaria; CCU = chronic cold urticaria; CindU = chronic inducible urticaria; CoU = cold urticaria; CSU = chronic spontaneous urticaria; CU = chronic urticaria; DLQI = Dermatology Life Quality Index ; IRA = idiopathic recurrent angioedema; ISS = itch severity score; QoL = Quality of Life; SU = solar urticaria; UAS-7 = 7-day urticaria activity score; UV = urticarial vasculitis.

^aData in parentheses are no. of patients with CIU or CSU/no. of patients without CIU or CSU.

^bData in parentheses are no. of patients receiving omalizumab/no. of patients receiving placebo.

Figure Legends

Figure 1. Schematic of the study selection process.

Figure 2. Possible mechanisms of action of omalizumab. IgE = immunoglobulin E.



