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Omalizumab Treatment in Chronic Inducible Urticaria: A Systematic Review of Published Evidence

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1 **Omalizumab Treatment in Chronic Inducible Urticaria: A Systematic Review**

2 **of Published Evidence**

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Abstract (<250 words; currently 200 [not including titles])

BACKGROUND: Omalizumab, a recombinant anti-IgE antibody, effectively treats chronic spontaneous urticaria. Evidence is lacking in chronic inducible urticarias (CIndUs), which are frequently H₁-antihistamine resistant.

OBJECTIVE: We aimed to determine, from the current published literature, the strength of evidence for omalizumab efficacy and safety in the treatment of CIndUs.

METHODS: We performed a PubMed® search to identify evidence on omalizumab use in the following nine CIndU subtypes: symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria and aquagenic urticaria.

RESULTS: 43 trials, case studies, case reports and analyses were identified. Our review indicates that omalizumab has substantial benefits in various CIndUs. The evidence is strongest for symptomatic dermographism, cold urticaria and solar urticaria. Little/no evidence was available on vibratory angioedema, aquagenic and contact urticaria. Our review supports the rapid onset of action, demonstrated through early symptom control in most cases, sometimes within 24 hours. Many patients gained complete/partial symptom relief and substantially improved quality of life. Adverse events were generally low with omalizumab being well tolerated by most patients including children.

CONCLUSIONS: A strong body of evidence supports the use of omalizumab in the treatment of patients with therapy-refractory CIndU. More data from randomised controlled studies are warranted.

Clinical Implications

Substantial evidence of omalizumab efficacy in chronic inducible urticaria exists. It has shown significant benefits in therapy-refractory patients and can provide a much needed option where antihistamine treatment has failed.

Abbreviations

CU, chronic urticaria

CSU, chronic spontaneous urticaria

CIndU, chronic inducible urticaria

QoL, quality of life

- 64 TPO, thyroid peroxidase
- 65 DLQI, Dermatology Life Quality Index
- 66 PGA, Patient Global Assessment
- 67 CU-Q₂OL, chronic urticaria quality of life questionnaire
- 68 AE, adverse event
- 69

Introduction

Chronic urticaria (CU), characterized by the recurrence of itchy wheals and/or angioedema for six weeks or longer, is divided into two types: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), of which there are several subtypes.(1) As the name suggests, the signs and symptoms of CIndUs are triggered by external factors specific for that subtype, such as sunlight in solar urticaria.

CIndUs are more prevalent than previously thought with up to 76% of CSU patients reporting a concurrent CIndU.(2) The presence of a CIndU has also been shown to be a predictor of severe CSU.(3) CIndUs are chronic, last several years, and often pose a great treatment challenge due to their resistance to first-line therapy with H₁-antihistamines.(4) CIndUs are debilitating, severely impacting quality of life (QoL),(5, 6) and yet it is normally not feasible to avoid the offending trigger without massive changes to everyday life. Thus, the need for treatment options is high.

The current treatment guidelines for CU aim for complete symptom control using a stepwise approach, starting with a standard dose of non-sedating H₁-antihistamines. Dosing can and should be increased up to 4-fold (which, however, represents an off-label use), because CIndU patients can benefit from up dosing.(7, 8) However, many patients do not,(1, 4) in which case, third line treatments including omalizumab are recommended.(1) Omalizumab, a recombinant humanized anti-IgE antibody, is now approved as add-on therapy in patients with H₁-antihistamine-refractory CSU, thus from clinical experience, it might be expected that patients with CIndU could also benefit.(9)

Current Evidence of Omalizumab in the Treatment of Chronic Urticaria

Omalizumab has been used to successfully treat CSU, with strong evidence coming from seven randomised controlled trials (10-16), a smaller study (17) and a meta-analysis.(18) However, omalizumab is not yet licensed for CIndUs and large-scale trials are lacking. The first reported case of omalizumab use in a CIndU was by J Boyce (19) in 2006 and, since this time, a body of evidence has accumulated in the form of trials, case studies, reports and retrospective analyses. Some research groups have recommended omalizumab to treat CIndU patients who cannot achieve adequate symptom control with conventional therapies.(20-22) Guideline recommendations for CSU are frequently adopted in the absence of good quality evidence for CIndUs.

In the current systematic review, we have aimed to determine, from the current published literature, existing evidence for efficacy and safety of omalizumab in the treatment of CIndUs. Some

rare, atypical forms of CIndU exist (i.e. cholinergic dermographism) but this review focuses on the nine major subtypes (see **Table 1**).

The Proposed Pathology of CIndU

The exact pathology of CIndU is yet to be fully elucidated, but the activation and degranulation of tissue-resident mast cells and the subsequent release of inflammatory mediators such as histamine play key roles.(23-25) As of now, it is unclear exactly what causes this activation and degranulation. Type I autoimmunity, sometimes also referred to as autoallergy, has been postulated to be a cause of CIndU.(26) In autoimmune type I urticaria, skin mast cells are activated by an IgE-mediated reaction to autoantigen. In CIndUs, the appropriate trigger results in *de novo* synthesized autoantigen (autoallergen), which is detected by IgE bound to skin mast cells, resulting in mast cell degranulation; this is supported by several independent lines of evidence.(26-28) Many patients with CU exhibit IgE autoantibodies directed against thyroid peroxidase (IgE-anti-TPO), and these patients have higher levels of total IgE, IgG-anti-TPO and lymphocyte counts in their serum/blood.(29) Some CIndUs such as symptomatic dermographism, solar urticaria and cold urticaria are transferable, with the transferable serum factor suggested being IgE.(30-33) Relevant autoantigens detected by IgE have been identified and characterized in part, e.g. in solar urticaria.(34) Desensitization, which works in cold urticaria and other CindUs, has been shown not to work via depletion of mast cells or mast cell mediators, but rather, it is suggested to work via depletion of the mast cell activating signal.(27)

Skin mast cell degranulation in solar urticaria, for example, occurs when skin is exposed to UV radiation. Mast cell degranulation is thought to involve IgE that is specific for photo-induced neoantigens that act as autoallergens. This IgE is bound to FcεRI, the high affinity IgE receptor on cutaneous mast cells, which gets activated by neoantigen-mediated crosslinking of IgE and the receptor. Because omalizumab blocks binding of IgE to FcεRI(35), it can intervene in this pathway, and mast cell activation and the inflammatory process are subsequently suppressed.

Method

We performed a MEDLINE® search (pubmed.com) to identify evidence of the use of omalizumab in each CIndU subtype, with no restrictions on time period covered or publication language. The advanced search option was used with the terms 'omalizumab' AND, for example, 'cold urticaria' to

encompass results from all fields. This was complemented by any additional published or in press evidence known to us at the time of publication (see **Table 2**).

In order to present a fair and unbiased account of the available published evidence, all publications have been included regardless of whether the results were positive or negative. Review articles have been excluded. Publications have been split into two groups based on the number of patients included in the report: case series or studies with ≥ 5 patients and case reports or small case series < 5 patients.

Results

We found overlap of CIndU subtypes between studies and, whilst many of the case studies presented include several patients, the numbers shown in **Table 2** relate only to the number of patients within the specified subtype.

A total of 43 trials, case studies, case reports and retrospective analyses on the use of omalizumab in CIndUs were identified and included in this review. Overall, three Phase II studies were identified in solar urticaria,(36) cold urticaria (37) and symptomatic dermographism (38) of which, the latter two were randomised and placebo-controlled. Most published evidence comes from single case reports, small case studies or larger case studies that also include some patients with CSU.

Overall, the vast majority of results indicate a beneficial role for omalizumab in each CIndU but evidence for certain subtypes was stronger than for others, as described under each heading below. To our knowledge, all doses of omalizumab were administered subcutaneously, as per the instructions. Adverse events were generally found to be low with omalizumab being well tolerated by most patients.

Physical urticaria

Symptomatic Dermographism

Symptomatic dermographism is the most common type of physical urticaria (39) with a prevalence of up to 5% in the general population.(40) It involves whealing and pruritus following minor stroking, rubbing or scratching of the skin, which can be unavoidable in daily life and can therefore substantially impair QoL.(41, 42) Antihistamines can be used to effectively treat the majority of patients but in some cases, further treatment is required.

We identified seven publications of omalizumab use in symptomatic dermographism encompassing a total of 72 patients (including 54 omalizumab- and 18 placebo-treated patients). The strongest evidence came from a randomised, placebo-controlled trial involving 55 patients with symptomatic dermographism, who had a high mean baseline Dermatology Life Quality Index (DLQI) score of 11.1, indicating a very high impact on QoL.(38) Results showed significant improvement in critical friction thresholds (the strongest trigger strength to induce symptoms) after ten weeks of treatment with 150mg (-1.8 ± 0.4 , $p=0.014$) and 300mg (-2.0 ± 0.4 , $p=0.004$) omalizumab vs. placebo-treated patients (-0.6 ± 0.3), with improvements observed as early as week four. No significant difference in efficacy was observed between the two omalizumab doses and efficacy was not affected by variations in baseline trigger thresholds or disease activity. After ten weeks of treatment, six of 18 (33%) patients on 150mg omalizumab and eight of 19 (42%) patients on 300mg omalizumab did not respond at all compared with 15 of 18 (83%) placebo-treated patients.(38)

A retrospective analysis showed 86% of patients achieved a complete response (absence of wheals after provocation testing/absence of symptoms assessed by Patient Global Assessment [PGA]) and 14% had a significant improvement ($\geq 50\%$ reduction in provocation thresholds/ $\geq 50\%$ improvement of symptoms).(43) Another analysis showed that one out of two patients achieved complete/almost complete response to treatment (44) and two further analyses by Metz *et al.* showed slightly differing results: in the first, one patient who received 300mg omalizumab, achieved complete symptom control but another patient, who began treatment on 150mg and then updosed to 300mg, did not.(45) Both patients had previously tried nine different medications to control their CIndU with little success. In the second analysis, all four patients (one with symptomatic dermographism plus CSU) gained complete symptom control with no need for additional medication after the first treatment.(46)

Finally, two case reports showed further positive results. In the first, a patient with antihistamine-refractory symptomatic dermographism who was treated with 300mg omalizumab every two weeks gained major reductions in pruritus and whealing within the first week, with complete symptom relief by the fourth week.(47) In the other, a patient with coexisting symptomatic dermographism, delayed pressure urticaria and CSU, achieved complete remission within 24 hours of receiving 150mg omalizumab.(48)

Cold Urticaria

Cold urticaria is the second most prevalent physical urticaria.(39) Wheals and/or angioedema develop within minutes of touching something cold and there is a serious risk of anaphylaxis or oropharyngeal oedema.(49-53)

Robust evidence exists for cold urticaria totalling 63 reported cases of omalizumab use (including 51 omalizumab- and 12 placebo-treated patients) across 11 publications. The first reported use was in 2006 in a 12-year-old patient with a 2-year history of cold urticaria and asthma.(19) The patient was given 375mg omalizumab every two weeks and after the second injection, could tolerate cold liquids with only mild pruritus. After five months, symptoms had completely disappeared and ice cube test responses were negative. Encouraging results from this case have been reinforced by a number of subsequent case reports.(45, 46, 53)

More recently, results from a randomised, placebo-controlled trial including 31 patients with cold urticaria demonstrated significant clinical superiority of omalizumab vs. placebo.(37) Because cold urticaria can be life-threatening and very limited/no efficacy was seen with placebo treatment, the study was terminated following interim result analysis. Mean changes in critical temperature thresholds (required to induce symptoms) after ten weeks were significantly higher in patients receiving 150mg ($-10.6^{\circ}\text{C} \pm 2.4$, $p=0.001$) and 300mg ($-10.4^{\circ}\text{C} \pm 3.1$, $p=0.013$) omalizumab compared with placebo ($-0.3^{\circ}\text{C} \pm 1.1$). Improvements were seen by week four. No significant difference in efficacy was observed between the two doses and variations in baseline critical temperature thresholds did not affect efficacy. After ten weeks of treatment, one of ten (10%) patients on 150mg omalizumab and two of nine (22%) patients on 300mg omalizumab were non-responders compared with nine of 12 (75%) placebo-treated patients.

Some case series also demonstrate substantial benefits; Kitsioulis *et al.* reported significant QoL improvements in five children with cold urticaria (children's DLQI score decreased by 41.46% [13.4–65.3%, $\text{SD}=18.66$]) after five months of treatment, while an improvement was observed after the first month (decrease range 17.65–40%, $\text{SD}=10.35$) in 80% of these patients.(54) Another set of cases showed that six patients all became symptom-free after treatment, with a significant decrease in cold stimulation tolerance tests.(55)

One case report showed significant improvements after an initial omalizumab injection and complete control after the second injection,(56) while another describes a 2-year-old patient who had experienced severe systemic reactions upon exposure to cold conditions, whose symptoms dramatically improved after treatment with 75mg omalizumab every four weeks.(57) However, two more reports suggest that only around half of patients included in an analyses responded well to omalizumab,(43, 44) and one case described a patient in which 300mg omalizumab treatment every

four weeks failed to adequately control symptoms and treatment was discontinued after eight months due to repeated fatigue and somnolence.(53)

Delayed Pressure Urticaria

Delayed pressure urticaria frequently coexists with CSU, but is rare as a primary inducible urticaria.(14) Due to its nature, the condition frequently goes unrecognized and can be difficult to attribute to a single trigger because symptoms typically occur 4–6 hours after, for example, wearing tight clothing, walking or sitting.(58) Lesions are painful and persist for up to three days. This subtype has been reported to cause significantly greater QoL impairment than other forms of urticaria (59) and it is normally unresponsive to high doses of antihistamines or corticosteroids.(60)

We identified 11 publications of omalizumab in delayed pressure urticaria involving 26 patients. The first reported use of omalizumab was by Bindslev-Jensen and Skov in a patient with a 10-year history whose previous medications (540mg fexofenadine and 100mg azathioprine per day) provided only partial relief, the benefits of which were gradually diminishing. Once 150mg omalizumab was started (given concomitantly with fexofenadine) total symptom relief was achieved after two days.(61) This was shortly followed by more case reports describing complete responders after just one injection.(45, 62, 63) In another case involving a patient with coexisting delayed pressure urticaria, symptomatic dermographism and CSU, complete remission was seen within 24 hours of 150mg omalizumab treatment (48) and three other cases reported the same result where a 300mg dose achieved complete symptom control within two days,(64, 65) and another within five days.(60)

Some reports however, showed mixed results: two patients with concurrent CSU and delayed pressure urticaria showed a complete remission after the first injection of omalizumab.(66) In a third patient with severe delayed pressure urticaria and CSU who had received ineffectual treatment for over 20 years, omalizumab reduced the symptoms of CSU but intensified those of delayed pressure urticaria, and the drug was withdrawn after two cycles. In the largest analysis including eight patients, seven (88%) achieved complete symptom control while one (12%) had significant improvements after treatment,(43) and another showed three out of five (60%) patients with a complete response.(44)

Solar Urticaria

Solar urticaria is a rare form of CIndU.(67) It is characterized by skin lesions at sites of photo-exposed skin, usually within minutes of ultraviolet (UV) radiation, including long wavelength UVA, short

wavelength UVB, and/or visible light.(68) It seriously impacts QoL and there is a risk of anaphylaxis should the entire body be exposed.(67, 69)

Of all CIndU subtypes, solar urticaria had the highest number of publications on omalizumab use. Of 18 publications which include 36 cases, the majority show that omalizumab successfully controlled symptoms, while four included patients with a partial response (43, 46, 70, 71) and three showed failure to respond to treatment.(44, 72, 73)

The strongest evidence came from a multicentre, prospective, Phase II study including ten antihistamine-refractory patients with solar urticaria that greatly impacted their QoL (DLQI score of >10).(36) Following three doses of omalizumab over an 8-week period, 20% of patients met the primary endpoint (95% confidence interval 2.52–55.6; $p=0.2639$), whereby symptoms were not triggered by a UV dose >10-fold the baseline minimal urticarial dose at week 12. Additionally, 40% of patients achieved a DLQI <6 and 40% achieved an improvement in severity (measured on a visual analogue scale) of 50%. No significant adverse events were experienced during the study.

Several case reports describe full remission of solar urticaria.(43, 45, 46, 74-80) Initial doses in these cases ranged from 150mg to 375mg, although in some patients, a higher dose of 450mg was necessary to achieve complete symptom control.(75, 81) Patients often relapsed 2–8 weeks after discontinuing treatment, but then responded well to the next omalizumab injection.(46) One case of omalizumab use in a 6-year-old child was reported following approval from an ethics committee for exceptional medical treatments.(82) An initial dose of 75mg did not achieve any apparent improvement therefore the dose was gradually increased to 300mg twice monthly, after which, complete remission was gained with no side effects.

In the cases of treatment failure, one patient received four doses of 150mg omalizumab every four weeks with no clinical improvement, and no changes in phototests although the authors speculate that a higher dose and longer treatment could have been more effective.(72) There was one report of worsening symptoms after three doses of 150mg omalizumab, indicating that this treatment is not suitable in all patients.(73)

Heat Urticaria

Heat urticaria is triggered by various forms of heat such as air, water or objects. It is an uncommon physical urticaria and difficult to effectively manage.(83) Avoiding all forms of heat poses a great challenge in everyday life and is often not feasible.

Evidence of omalizumab use in heat urticaria is limited and comes from just four publications covering five case reports. Two patients seriously affected by their condition whose symptoms were insufficiently controlled by conventional treatments achieved marked clinical improvements after the first doses of 300mg omalizumab.(84) In one of these cases, the heat application test became negative. In another case report, almost complete symptom control was achieved after a patient received four doses of omalizumab alternating between 300mg and 450mg biweekly.(20) The 450mg dose achieved greater symptom improvement compared with 300mg, and the patient received a total of 38 doses with no side effects, and no need for concomitant medication.

Two other case reports described less favourable responses with either no significant improvement,(43) or only minor improvements in one patient with an extremely treatment-resistant form of heat urticaria, as indicated by nine prior medications including loratadine, cetirizine and montelukast.(45)

Vibratory Angioedema

Vibratory angioedema, a very rare form of CIndU, is characterized by the eruption of pruriginous erythema within minutes of vibratory contact to the skin.(4) It is typically induced by vibratory motions such as running or using an electric lawnmower or pneumatic drill.

Only one case report of omalizumab use in vibratory angioedema was found, which failed to improve symptoms.(85)

Other inducible urticaria

Cholinergic Urticaria

Cholinergic urticaria is characterized by pin-sized wheals with surrounding erythema and extreme pruritus. Symptoms are induced by increases in core body temperature through, for example, physical exercise or emotional stress. In most cases, symptoms are mild to moderate, but sometimes wheals cover the entire body and antihistamines are often ineffectual.(86)

One case series involving eight patients (43) and six smaller case reports/series (44, 46, 87-90) were identified for omalizumab use in cholinergic urticaria, totalling 20 reported cases. The retrospective analysis by Metz *et al* showed that 62% of patients achieved a complete response (absence of wheals after provocation testing/absence of symptoms assessed by PGA), 13% had a significant improvement ($\geq 50\%$ reduction in provocation thresholds/ $\geq 50\%$ improvement of symptoms) and 25%

showed no significant improvement (<50% reduction in provocation thresholds/ improvement of symptoms).(43) Most patients began on 150mg omalizumab with one on 300mg. Another analysis showed greater benefits; three patients with cholinergic urticaria and one with cholinergic urticaria plus cold urticaria achieved complete symptom control with no need for any concomitant medication.(46) Disease relapsed within 2–8 weeks of omalizumab discontinuation, despite patients taking antihistamines. In another study, 75% of patients achieved complete responses with omalizumab therapy.(44)

Three case studies indicated great improvement of symptoms: two cases describe patients' symptoms drastically improving after only one dose of omalizumab, as measured by the DLQI and a CU-QoL questionnaire (CU-Q₂OL), respectively.(88, 90) In addition, one patient had also been suffering from severe dyspeptic complaints, which almost completely disappeared.(90) In another case, a patient significantly improved after the second injection of 300mg omalizumab and concomitant medication was reduced.(87)

One case is reported of a patient whose symptoms were unresponsive to 300mg omalizumab treatment given every two weeks although the author speculates that lack of response may be related to high IgE levels, and a higher dose might have produced more successful results.(89)

Contact Urticaria

Contact urticaria is characterized by wheals and angioedema that occur in response to contact with urticariaogenic substances. Mast cell activation is either non-immunologic, i.e. without prior sensitization to the eliciting agent or immunologic, i.e. IgE-mediated.(91) We did not identify any reported uses of omalizumab in contact urticaria.

Aquagenic Urticaria

Aquagenic urticaria is a rare inducible CIndU, which occurs when the skin is exposed to water, including sweat and tears. Patients typically present with 1–3 mm wheals with surrounding 1–3 cm erythematous flares within minutes of water contact.(83) In some cases, symptoms can be more severe and include wheezing or shortness of breath. The nature of this subtype has obvious impact on QoL as simple activities such as bathing can become almost impossible. Many patients are refractory to H₁-antihistamines and require further interventions.

Only one case of omalizumab treatment in aquagenic urticaria was identified.(92) A patient with a 2-year history of aquagenic urticaria whose condition was uncontrolled by previous medications

including montelukast, cetirizine, loratadine, ranitidine, diphenhydramine and hydroxyzine was started on omalizumab 300mg per month. Symptoms completely resolved following two omalizumab doses, she was able to go swimming for the first time in many years and discontinued other medications without symptom recurrence.

Adverse Events

Overall, instances of adverse events (AEs) were low and rarely led to treatment discontinuation. In one study involving a mixture of CSU and CIndU patients, 14% of patients overall reported AEs during treatment including suspected allergic reactions, gastrointestinal symptoms, injection site reactions, worsening urticaria, headache, dizziness, arthritis and fatigue.(44) In another analysis of 51 patients (again, including both CSU and CIndU patients) no unwanted side effects were reported from omalizumab, except one case where treatment was discontinued following mild cutaneous angioedema several hours after administration.(43) In the two placebo controlled randomized trials in patients with cold urticaria and symptomatic dermographism, the frequency of AEs was similar between omalizumab and placebo groups.(37) One patient with cold urticaria discontinued treatment due to inadequate symptom control and AEs including fatigue and somnolence.(53) In order to prospectively monitor AEs in CIndU patients, an investigator-initiated urticaria registry has been set up to track chronic urticaria patients (<http://www.urticaria-registry.com/>). This has now almost reached its 1,000th patient and will provide valuable future data to record AEs and efficacy of all urticaria treatments.

Conclusions

A large body of evidence has accumulated of omalizumab use in CIndUs since the first reported use in 2006.(19) Two randomised controlled trials, several sizable case series and many case reports exist to indicate that omalizumab provides substantial benefits in various CIndU, but more data on efficacy and safety from controlled (licensing) studies are needed.

The dose of omalizumab used appears to be important based on individual patient needs; due to the nature of this review which includes all published evidence (excluding review articles), a range of different doses was used across the studies. Some studies showed no apparent difference between omalizumab doses (37, 38) while in many, a lower dose of 150mg was sufficient to elicit a good response (37, 38, 48, 61) and in others, higher doses generally appeared to be more efficacious, which is supported by previous evidence.(18) Depending on the type of CIndU, the age and weight of

the patient, doses should be tailored to individual patient needs. In some of the reported treatment failures, it was speculated that a higher dose could have produced more success and in some cases, the benefits of up dosing to reach maximal effects were apparent.(75, 81)

Differences between omalizumab treatment in CIndU vs. CSU patients were discovered, with the dose required to gain a response being the major difference between the two populations. Most randomised trials in CSU have involved omalizumab doses of between 75 – 600 mg, with the majority of patients treated with a 300 mg dose.(10-16) The effective dose in CSU appears to plateau at around 300 mg, with 75 mg having failed to show a meaningful response, and doses beyond 300 mg generally not showing greater efficacy in omalizumab naïve-patients. However, this differed in CIndU responses to omalizumab. The two randomised trials in symptomatic dermographism(38) and cold urticaria(37) both tested 150 mg and 300 mg in the relevant patients but no significant differences between the doses were observed at any time during the study, indicating that the lower dose of 150 mg may be more appropriate in this patient population. This requires further investigation including studies that confirm earlier results showing that omalizumab up dosing effective in CIndU patients (and CSU patients) who fail to respond to their initial dose of omalizumab. (43)

One common theme identified was that many patients had already tried several medications in an attempt to control their urticaria symptoms and for some, most treatment options had been exhausted. Considering this, omalizumab provided at least partial, if not complete, relief for the majority of these patients after several years of discomfort.

Published clinical trials demonstrate that response to omalizumab in CSU is evident within the first weeks of treatment (10, 13) and our review also supports the rapid onset of action in CIndUs, demonstrated through early symptom control recorded in most publications. However, the question of time to response is important and not all patients respond to treatment in the same manner and at the same speed. Time to response has been shown to differ between patients and future characterization of predictive factors may lead to better prognosis and treatment of distinct patient groups.(93) A recent study in CSU has shown that the majority of patients respond within the first eight days, with around one third responding on day one (93) and around 12% not responding. Similar studies are needed for CIndUs.

One publication was identified where patients received more than one course of omalizumab treatment.(46) A total of 16 patients with five different CIndUs (some with coexisting CSU) were treated with omalizumab doses between 150 mg and 600 mg/month and disease activity was determined by trigger threshold testing or by the patient's history. All patients achieved complete

symptom control ($\geq 90\%$ improvement) during the first course of treatment. Once discontinued, all patients experienced a relapse of disease, despite antihistamine treatment, within 2 – 8 weeks after their last omalizumab injection (except for two patients who relapsed after 4 and 7 months). Retreatment was started at the same dose and regimen of omalizumab as the last successful treatment before discontinuation. Upon the first re-injection of omalizumab, all patients responded completely and rapidly within 4 weeks, but more commonly, during the first days of retreatment. This was the only publication to specifically investigate relapse of CIndUs and how these patients responded to omalizumab upon reinitiation. Interestingly, no patients in this study reported AEs other than mild injection site reactions during either the initial use or during retreatment.

Variation of omalizumab use was seen between the CIndU subtypes, with the most thorough evidence available in cold urticaria (complete/partial response in 41 out of 51 patients), symptomatic dermographism (complete/partial response in 38 out of 54), and solar urticaria (complete/partial response in 28 out of 36 patients), with the level of complete responders observed in cold urticaria patients comparable to the efficacy reported from clinical trials with CSU.⁽⁹⁴⁾ Little or no evidence was available on vibratory angioedema, aquagenic and contact urticaria and, therefore, the use of omalizumab and its outcome in patients with these CIndUs should be documented and reported.

Several cases were identified of omalizumab use in children,^(54, 63, 82) and one case in a pregnant woman, with no unexpected side effects and no complications or harm to the unborn child.⁽⁴⁸⁾

We acknowledge that omalizumab is a costly treatment option compared to some alternative treatments. As yet, no health economic data exists to compare its cost with the health, psychological and economic burden of lost working days due to CIndUs.

Other drugs that target IgE are in development, such as the monoclonal IgG₁ antibodies ligelizumab and quilizumab, which should be assessed for their effects in CIndU.⁽⁹⁵⁾

Our review is limited by the important but unavoidable fact that results could be potentially biased as we only identified published reports based on our specific MEDLINE® search criteria and failed uses of omalizumab are a lot less likely to have been reported in the literature. This is a relevant point but is very difficult to control for in systematic reviews of this nature. We did, however, find two reports of omalizumab failure in CIndUs and another report where a patient with cold urticaria had to discontinue treatment due to inadequate symptom control and adverse events.⁽⁵³⁾ This indicates that some, but probably not all, negative results have been published.

Due to the fact that in many patients CIndUs are not controlled by conventional H₁-antihistamines, an unmet need exists for further controlled, randomised trials in all CIndUs, with special attention

paid to those in which high quality evidence is lacking. Additionally, further mechanistic studies are required to determine the pathophysiology of CIndU.

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Conflicts of Interest

Maurer: Consultant/speaker and/or recipient of institutional funding of research or clinical trials: Alarez, Allakos, FAES, Genentech, MOXIE, Novartis, Sanofi, Uriach.

Metz: Consultant/speaker: Bayer, GSK, Moxie, Novartis, Roche, Sanofi, Shire

Brehler: Consultant/speaker and/or clinical trials: ALK, Allergopharma, Almirall, Astra Zeneca, Bencard, Circassia, GSK, Dr. Pflieger, Leti, Novartis, Pierre Fabre, Pohl Boskamp, Siemens, Stallergenes, Thermo-Fischer

Hillen: Consultant/speaker and recipient of research grant: Novartis

Jakob: Consultant/speaker: ALK-Abelló, Allergy Therapeutics, Allergopharma, Novartis, Stallergenes, Thermo Fisher. Research grants: ALK-Abello, Allergopharma, Cormetics Europe, Novartis, Thermo Fisher Scientific. Executive Board member: German Society of Allergy and Clinical Immunology. Editor: Allergo Journal International (Springer)

Mahler: Consultant/speaker and/or recipient of institutional funding of research or clinical trials during the last 3 years from Allergy Therapeutics, ALK-Abelló, Glaxo SmithKline, HAL, Novartis, Thermo Fisher.

Pföhler: Consultant/Speaker: ALK abello, Bencard, GSK, Novartis, Stallergenes, MSD, Roche, Celgene, Leo, Abbvie, Amgen. Clinical trials: Bencard/Allergy Therapeutics

Staubach: Consultant/Speaker Novartis, Celgene, Astellas, MSD, UCB, Pflieger, MSD, Karrer, Pohl, Leti, Leo, Shire, Abbvie, Sobi, CSL Behring, Pfizer, Janssen, Lilly."

Treudler: Consultant/speaker and/or clinical trials: ALK-Abello, Novartis, Shire. Fees for lectures and/or advisory boards: ALK-Abello, Novartis, Shire.

Wedi: Consultant/speaker: ALK-Abelló, Stallergenes, Novartis, Dr. Pflieger, Astellas, Shire, Celgene,
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 Magerl: Consultant/speaker: Moxie, Novartis

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Figure and Table Legends

Figure 1. The Inflammation of Mast Cells in Chronic Inducible Urticaria. Mast cell inflammation is the final pathway that leads to urticaria symptoms. Free IgE binds to FcεRI receptors on mast cells, thereby activating the cells to release pro-inflammatory/pathological mediators

Figure 2. Responses to Omalizumab Treatment in Various CIndUs. Cases from all 43 identified publications are included. Two trials on cold urticaria and symptomatic dermographism were placebo-controlled (placebo results shown as a separate bar)

Table 1: Classification of Urticarias Subtypes. € also called urticaria factitia, dermographic urticaria; § also called cold contact urticaria; ∞ also called pressure urticaria; ¥ also called heat contact urticaria

Table 2. Published Evidence of Omalizumab Use in Various CIndUs

Tables

1

Chronic Inducible Urticaria	Chronic Spontaneous Urticaria
<u>Physical urticaria</u> • Symptomatic Dermographism€ • Cold Urticaria§ • Delayed Pressure Urticaria∞ • Solar Urticaria • Heat Urticaria¥ • Vibratory Angioedema <u>Other inducible urticaria</u> • Cholinergic Urticaria • Contact Urticaria • Aquagenic Urticaria	Spontaneous appearance of itchy wheals, angioedema, or both ≥6 weeks due to known or unknown causes

Physical Urticarias		
	Case series or studies with ≥5 patients	Case reports or small case series <5 patients
Symptomatic Dermographism	- Maurer M, Schütz A, <i>et al.</i> Omalizumab is effective in symptomatic dermographism – results of a randomized, placebo controlled trial. <i>J Allergy Clin Immunol</i> 2017: in press (1) 55 patients - Metz M, Ohanyan T, <i>et al.</i> Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. <i>J Dermatol Sci</i> 2014; 73: 57–62 (2) Seven patients	- Ghazanfar MN, Sand C, <i>et al.</i> Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. <i>Br J Dermatol</i> 2016;175:404-6 (3) Two patients - Krause K, Ardelean E, <i>et al.</i> Antihistamine-resistant urticaria factitia successfully treated with anti-immunoglobulin E therapy. <i>Allergy</i> 2010;65(11):1494–5 (4) One patient - Metz M, Altrichter S, <i>et al.</i> Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. <i>Int Arch Allergy Immunol</i> 2011;154(2):177–80 (5) Two patients - Metz M, Ohanyan T, <i>et al.</i> Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. <i>JAMA Derm</i> 2014;150: 288–290 (6) Four patients - Vieira dos Santos R, Locks Bidese B, <i>et al.</i> Effects of omalizumab in a patient with three types of chronic urticaria. <i>Brit J Dermatol</i> 2014;170:469-471. doi: 10.1111/bjd.12628. (7) One patient (with coexisting symptomatic dermographism, delayed pressure urticaria and CSU)
Cold Urticaria	- Metz M, Schütz A, <i>et al.</i> Omalizumab is effective in cold urticaria – results of a randomized, placebo controlled trial. <i>J Allergy Clin Immunol</i> 2017: in press (8) 31 patients - Ghazanfar MN, Sand C, <i>et al.</i> Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. <i>Br J Dermatol</i> 2016;175:404-6 (3) Five patients - Kitsioulis NA, Xepapadaki P, <i>et al.</i> Omalizumab in pediatric cold contact urticaria: warm blanket for a cold bath? <i>Pediatr Allergy Immunol</i> 2016;27(7):752-755. doi: 10.1111/pai.12609 (9) Five patients - Metz M, Ohanyan T, <i>et al.</i> Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. <i>J Dermatol Sci</i> 2014;73: 57–62 (2) Six patients - Sussman G, Hébert J, <i>et al.</i> Real-life experiences with omalizumab for the treatment of chronic urticaria. <i>Ann Allergy Asthma Immunol</i> 2014; 112(2):170–4 (10) Six patients	- Alba Marín JC, Martorell Aragones A, <i>et al.</i> Treatment of Severe Cold-Induced Urticaria in a Child With Omalizumab. <i>J Investig Allergol Clin Immunol</i> 2015;25:303-4 (11) One patient - Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. <i>J Allergy Clin Immunol.</i> 2006; 117(6):1415–8 (12) One patient - Brodská P, Schmid-Grendelmeier P. Treatment of severe cold contact urticaria with omalizumab: case reports. <i>Case Rep Dermatol</i> 2012;4(3):275–80. doi: 10.1159/000346284 (13) Two patients - Le Moing A, Bécourt C, <i>et al.</i> Effective treatment of idiopathic chronic cold urticaria with omalizumab: report of 3 cases. <i>J Am Acad Dermatol</i> 2013;69(2):e99–101 (14) Three patients - Metz M, Altrichter S, <i>et al.</i> Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. <i>Int Arch Allergy Immunol</i> 2011;154(2):177–80 (5) One patient - Metz M, Ohanyan T, <i>et al.</i> Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. <i>JAMA Derm</i> 2014;150: 288–290 (6) Two patients (including one patient with cold urticaria and cholinergic urticaria)
Delayed Pressure Urticaria	Ghazanfar MN, Sand C, <i>et al.</i> Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. <i>Br J Dermatol</i> 2016;175:404-6 (3) Five patients	- Bindslev-Jensen C, Skov PS. Efficacy of omalizumab in delayed pressure urticaria: a case report. <i>Allergy</i> 2010;65(1):138–9 (15) One patient - Geller M. Successful treatment of occupational delayed pressure urticaria and angioedema with omalizumab. <i>Ann Allergy Asthma Immunol</i> 2016;116:81-2. doi: 10.1016/j.anai.2015.10.009 (16) One patient

	Metz M, Ohanyan T, <i>et al.</i> Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. <i>J Dermatol Sci</i> 2014; 73: 57–62 (2) Eight patients	- Kasperska-Zajac A, Jarzab J, <i>et al.</i> Effective treatment of different phenotypes of chronic urticaria with omalizumab: Case reports and review of literature. <i>Int J Immunopathol Pharmacol</i> 2016;29:320-8. doi: 10.1177/0394632015623795 (17) Three patients (all with coexisting CSU) - Metz M, Altrichter S, <i>et al.</i> Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. <i>Int Arch Allergy Immunol</i> 2011;154(2):177–80 (5) One patient - Metz M, Ohanyan T, <i>et al.</i> Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. <i>JAMA Derm</i> 2014;150: 288–290 (6) Six patients (five with delayed pressure urticaria and CSU) - Müller S, Rafei-Shamsabadi D, <i>et al.</i> Bullous Delayed Pressure Urticaria Responding to Omalizumab. <i>Acta Derm Venereol</i> 2016;96(3):416-7. doi: 10.2340/00015555-2224 (18) One patient - Quintero OP, Arrondo AP, <i>et al.</i> Rapid response to omalizumab in 3 cases of delayed pressure urticaria. <i>J Allergy Clin Immunol Pract</i> 2017;5(1):179-180. doi: 10.1016/j.jaip.2016.07.016 (19) Three patients - Rodríguez-Rodríguez M, Antolin-Amerigo D, <i>et al.</i> Successful treatment of severe delayed pressure angio-oedema with omalizumab. <i>Allergol Immunopathol (Madr)</i> 2014;42:78-80. doi: 10.1016/j.aller.2012.11.001 (20) One patient - Netchiporouk E, Nguyen CH, <i>et al.</i> Management of pediatric chronic spontaneous and physical urticaria patients with Omalizumab: case series. <i>Pediatr Allergy Immunol</i> 2015;26:585-588. doi: 10.1111/pai.12407 (21) One patient (with delayed pressure urticaria and CSU) - Vieira dos Santos R, Locks Bidese B, <i>et al.</i> Effects of omalizumab in a patient with three types of chronic urticaria. <i>Brit J Dermatol</i> 2014;170:469-471. doi: 10.1111/bjd.12628. (7) One patient (with coexisting delayed pressure urticaria, symptomatic dermatographism and CSU)
Solar Urticaria	Aubin F, Avenel-Audran M, <i>et al.</i> Omalizumab in patients with severe and refractory solar urticaria: A phase II multicentric study. <i>J Am Acad Dermatol. J Am Acad Dermatol.</i> 2016;74(3):574-5. doi: 10.1016/j.jaad.2015.11.021 (22) Ten patients	- Araši S, Crisafulli G, <i>et al.</i> Treatment with omalizumab in a 16-year-old Caucasian girl with refractory solar urticaria. <i>Pediatr Allergy Immunol</i> 2015;26(6):583–5 (23) One patient - Baliu-Piqué C, Aguilera Peiró P. Three cases of solar urticaria successfully treated with omalizumab. <i>J Eur Acad Dermatol Venereol</i> 2016;30(4):704-6. doi: 10.1111/jdv.13001 (24) Three patients - Brüning JH, Ziemer M, <i>et al.</i> Successful treatment of solar urticaria with omalizumab. <i>J Dtsch Dermatol Ges</i> 2016;14:936-7. doi: 10.1111/ddg.13017 (25) One patient - Combalia A, Fernández-Sartorio C, <i>et al.</i> Refractory solar urticaria successfully treated with omalizumab with normalization of phototest. <i>Actas Dermosifiliogr</i> 2017. pii: S0001-7310(17)30013-3. doi: 10.1016/j.ad.2016.11.015 (26) One patient - de Dios-Velázquez Á, González-de Arriba M, <i>et al.</i> Effectiveness of omalizumab in severe solar urticaria. <i>Ann Allergy Asthma Immunol</i> 2016;116:260. doi: 10.1016/j.anai.2015.12.023 (27) One patient - Duchini G, Bäumler W, <i>et al.</i> Failure of omalizumab (Xolair®) in the treatment of a case of solar urticaria caused by ultraviolet A and visible light. <i>Photodermatol Photoimmunol Photomed</i> 2011;27(6):336-7. doi: 10.1111/j.1600-0781.2011.00624.x (28) One patient - Ghazanfar MN, Sand C, <i>et al.</i> Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. <i>Br J Dermatol</i> 2016;175:404-6 (3) One patient - Guzelbey O, Ardelean E, <i>et al.</i> Successful treatment of solar urticaria with anti-immunoglobulin E therapy. <i>Allergy</i>

		2008;63(11):1563–5 (29) One patient ▪ Kowalick L, Thiel W, <i>et al.</i> Partial response of solar urticaria to omalizumab therapy. <i>Hautarzt</i> 2016 Epub ahead of print (30) One patient ▪ Levi A, Tal Y, <i>et al.</i> Successful omalizumab treatment of severe solar urticaria in a 6-year-old child. <i>Pediatr Allergy Immunol.</i> 2015;26(6):588–90 (31) One patient ▪ Metz M, Altrichter S, <i>et al.</i> Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. <i>Int Arch Allergy Immunol</i> 2011;154(2):177–80 (5) Two patients ▪ Metz M, Ohanyan T, <i>et al.</i> Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. <i>JAMA Dermatol</i> 2014;150: 288–290 (6) One patient ▪ Metz M, Ohanyan T, <i>et al.</i> Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. <i>J Dermatol Sci</i> 2014;73: 57–62 (2) Four patients ▪ Moncourier M, Assikar S, <i>et al.</i> Visible light-induced solar urticaria is improved by omalizumab. <i>Photodermatol Photoimmunol Photomed</i> 2016;32(5-6):314–316. doi: 10.1111/phpp.12271 (32) Four patients ▪ Müller S, Schempp CM, <i>et al.</i> Failure of omalizumab in the treatment of solar urticaria. <i>J Eur Acad Dermatol Venereol</i> 2016;30(3):524–5. doi: 10.1111/jdv.12922 (33) One patient ▪ Terrani I, Bircher AJ, <i>et al.</i> Solar urticaria induced by visible light: successful treatment with omalizumab. <i>Clin Exp Dermatol</i> 2016;41(8):890–892. doi: 10.1111/ced.12951 (34) One patient ▪ Waibel KH, Reese DA, <i>et al.</i> Partial improvement of solar urticaria after omalizumab. <i>J Allergy Clin Immunol</i> 2010;125(2):490–1. doi: 10.1016/j.jaci.2009.11.007 (35) One patient
Heat Urticaria	NA	▪ Bullerkotte U, Wieczorek D, <i>et al.</i> Effective treatment of refractory severe heat urticaria with omalizumab. <i>Allergy</i> 2010;65(7):931–2 (36) One patient ▪ Carballada F, Nuñez R, <i>et al.</i> Omalizumab treatment in 2 cases of refractory heat urticaria. <i>J Investig Allergol Clin Immunol</i> 2013;23(7):519–21 (37) Two patients ▪ Metz M, Altrichter S, <i>et al.</i> Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. <i>Int Arch Allergy Immunol</i> 2011;154(2):177–80 (5) One patient ▪ Metz M, Ohanyan T, <i>et al.</i> Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. <i>J Dermatol Sci</i> 2014: 73: 57–62 (2) One patient
Vibratory Angioedema	NA	▪ Pressler A, Grosber M, <i>et al.</i> Failure of omalizumab and successful control with ketotifen in a patient with vibratory angio-oedema. <i>Clin Exp Dermatol</i> 2013;38:151–3. doi: 10.1111/j.1365-2230.2012.04430.x (38) One patient
Other inducible urticaria		

Cholinergic Urticaria	Metz M, Ohanyan T, <i>et al.</i> Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. <i>J Dermatol Sci</i> 2014;73; 57–62 (2) Eight patients	- Ghazanfar MN, Sand C, <i>et al.</i> Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. <i>Br J Dermatol</i> 2016;175:404-6 (3) Four patients - Kutlu A, Tanoglu A, <i>et al.</i> Healing effects of omalizumab in a patient with cholinergic urticaria associated severe dyspeptic complaints. <i>Chin Med J (Engl)</i> 2015;128(11):1559-60. doi: 10.4103/0366-6999.157703 (39) One patient - Metz M, Ohanyan T, <i>et al.</i> Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. <i>JAMA Derm</i> 2014;150; 288–290 (6) Four patients (including one patient with cholinergic urticaria and cold urticaria) - Metz M, Bergmann P, <i>et al.</i> Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. <i>Allergy</i> 2008 Feb;63(2):247–9 (40) One patient - Otto HF, Calabria CW. A case of severe refractory chronic urticaria: a novel method for evaluation and treatment. <i>Allergy Asthma Proc</i> 2009;30(3):333-7. doi: 10.2500/aap.2009.30.3237 (41) One patient - Sabroe RA. Failure of omalizumab in cholinergic urticaria. <i>Clin Exp Dermatol</i> 2010;35(4):e127-9. doi: 10.1111/j.1365-2230.2009.03748.x (42) One patient
Contact Urticaria	NA	NA
Aquagenic Urticaria	NA	Rorie A, Gierer S. A case of aquagenic urticaria successfully treated with omalizumab. <i>J Allergy Clin Immunol Pract</i> 2016;4(3):547-8. doi: 10.1016/j.jaip.2015.12.017 (43) One patient

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43. Rorie A, Gierer S. A case of aquagenic urticaria successfully treated with omalizumab. *J Allergy Clin Immunol Pract*. 2016;4(3):547-8.

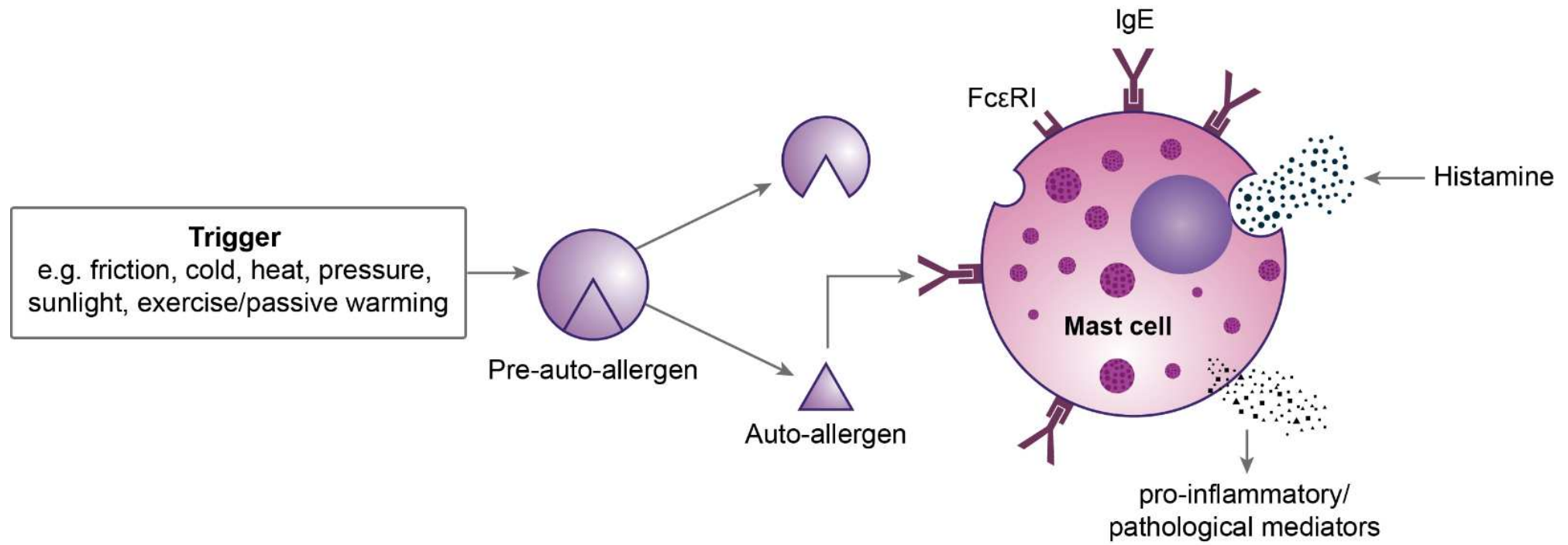


FIGURE 1

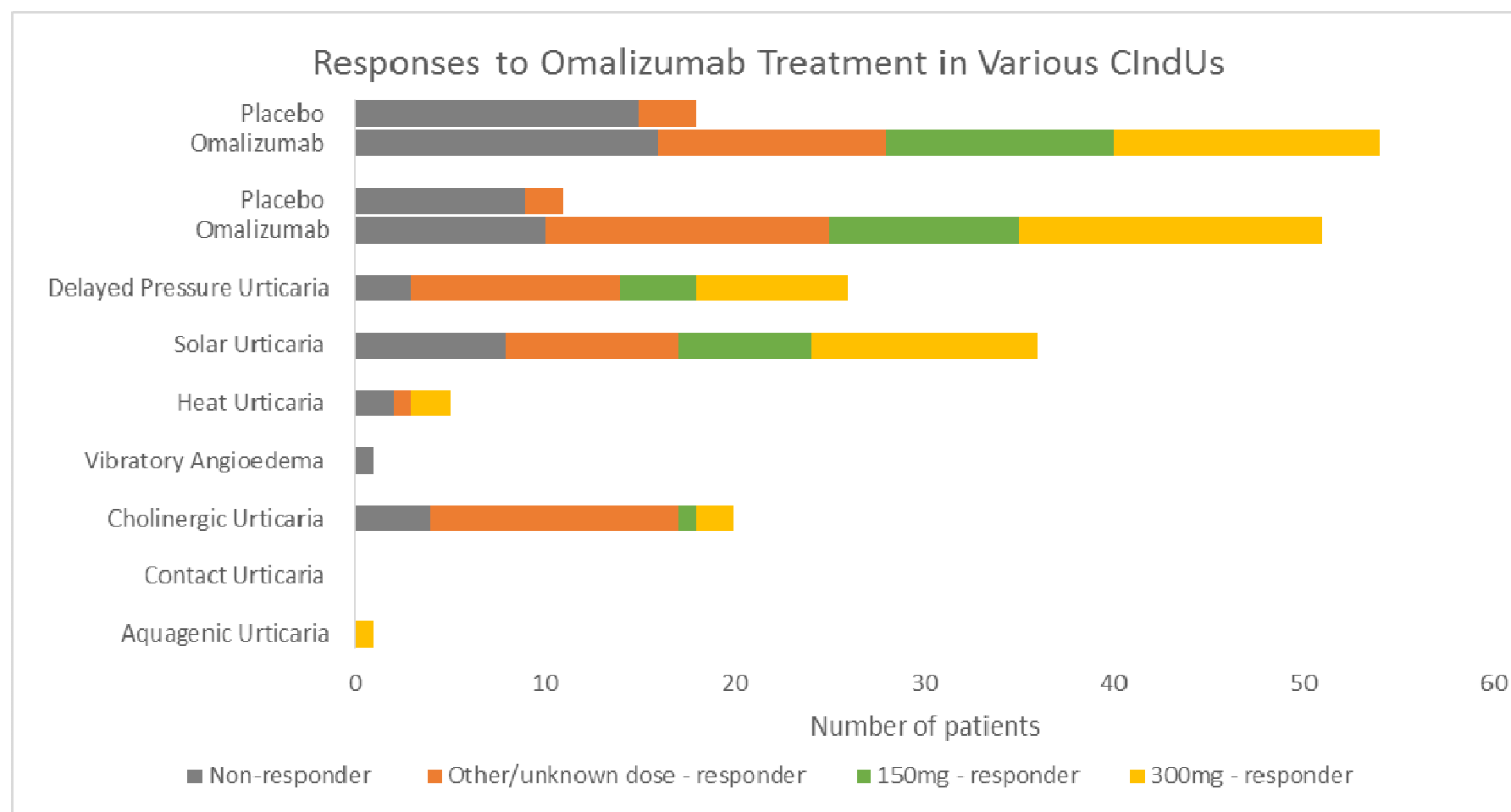


FIGURE 2