Chapter

The Role of Anti-IgE Antibodies in Urticaria

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Abstract

Chronic urticaria, a common mast cell driven disease, has been considered so far an underestimated and difficult to treat disease, very often resulting in high physical, psychological and socio-economic burden. More than 60% of these patients are unresponsive to second generation H1 antihistamines, the first-line symptomatic treatment for urticaria. However, anti-IgE drugs (omalizumab and ligelizumab) showed improved activity in urticaria-treated patients with inadequate symptom control. Omalizumab has been widely proven to be very effective and well-tolerated in patients with antihistamine-refractory chronic spontaneous urticaria and inducible urticaria and is currently licensed for these indication as third-line treatment. Ligelizumab, a next-generation monoclonal anti-IgE antibody with higher affinity to IgE compared to omalizumab and a similar safety profile, has recently demonstrated to be even more effective than omalizumab. This review is focused on the role of anti-IgE antibodies in chronic urticaria.

Keywords: Urticaria, Chronic Spontaneous Urticaria, Chronic Inducible Urticaria, Anti-IgE antibodies, Omalizumab, Ligelizumab

1. Introduction

Urticaria is a common mast cell-driven disease characterised by wheals (1–24 hours) and/or angioedema (up to 72 hours) (**Figure 1**), defined as acute when symptoms last <6 weeks or chronic if they occur continuously or intermittently for ≥6 weeks [1]. Approximately 50% of patients have both hives and angioedema, whereas 40% have wheals alone, and 10% have angioedema alone [2]. Moreover, Chronic Urticaria (CU) can be further classified as Chronic Inducible Urticaria (CIndU) when appear in response to specific eliciting factors, such as thermal agents, vibration, cholinergic factors, aquagenic, and delayed pressure or as Chronic Spontaneous Urticaria (CSU) if the above mentioned triggers have been excluded [1].

1.1 The prevalence of Chronic Urticaria

Both children and adults may develop urticaria, with the peak age of onset in adults being between 20 and 40 years [2]. The lifetime prevalence of Acute Urticaria (AU) ranges from <1% to 24% (12% to 24% in Europe), depending on the age range, method of sampling, and geographic location [3]. Instead, CU is estimated at 1% but there is no reliable data regarding its prevalence due to the lack of cross-sectional studies [4]. About 20% to 45% of patients with AU develop into CU.

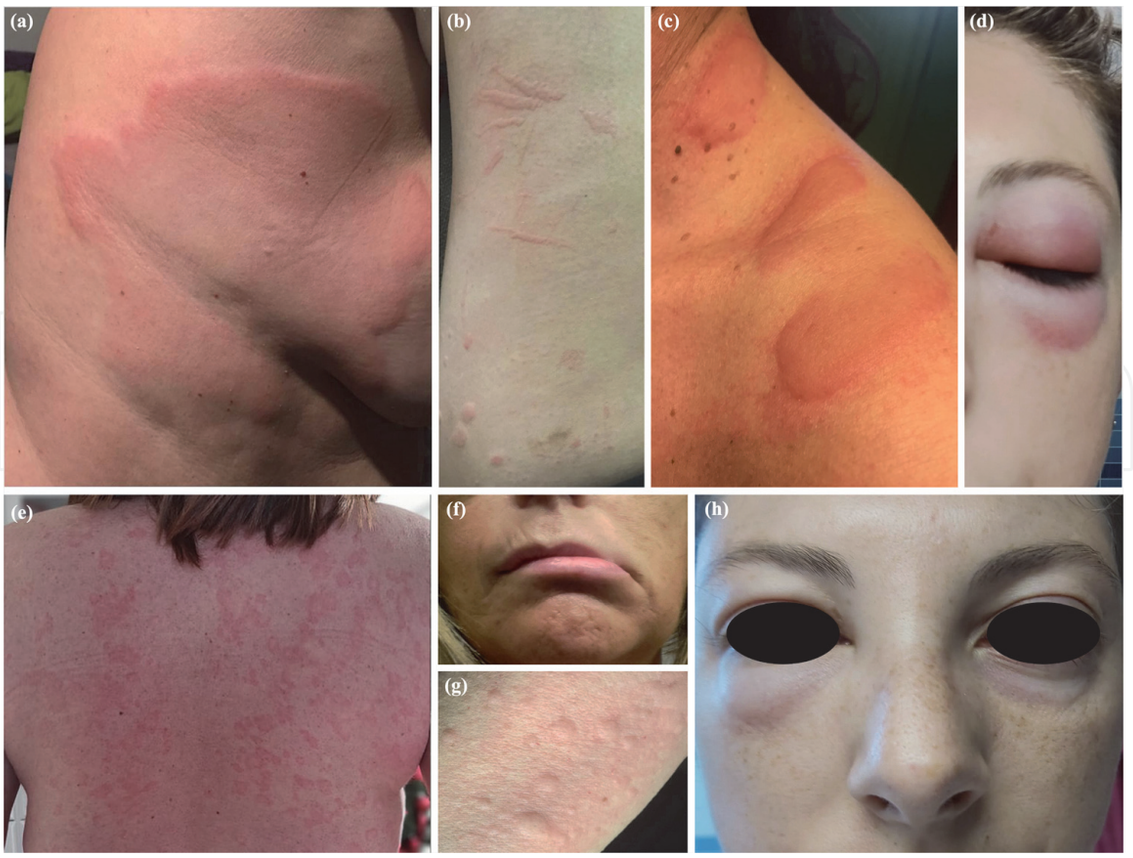

Figure 1.
(a–h): Urticaria is characterised by an outbreak of swollen, pale red bumps or plaques on the skin (wheals) and can also manifest as deep swelling around the eyes, lips, and face (angioedema) that appears suddenly.

CSU occurs in 0.5–1% of the population at any point in time, with its incidence peaking between 20 and 40 years of age [5]. CSU is considered more common in adults than in children and women are affected twice as often as men. However, recent studies have suggested that the prevalence of CSU in the paediatric population is similar to that of the adult population [6].

Finally, the CIndU prevalence is lower than other types of urticaria (e.g., acquired cold urticaria in Europe is extimated around 0.5%) [3].

1.2 The burden of Chronic Urticaria

In 1997 O'Donnel et al. compared the Quality of Life (QoL) scores in 142 patients with CU and 98 patients with life-threatening heart disease, finding similar QoL scores in both groups [7]. Indeed, many CU patients exhibit a severe impairment of their quality of life. The long disease duration (on average aorund two to five years) and the lack of curative therapy have been underlined as the two main aspects that contribute to the high physical, psychological and socio-economic burden of CU [8, 9]. The last EAACI/GA^{2}LEN/EDF/WAO guideline recommends "aiming at complete symptom control in urticaria, considering as much as possible the safety and the QoL of each individual patient" [1]. Currently, two specific QoL questionnaires are available for evaluating the burden of CU on patients: Chronic Urticaria Quality of Life (CU-Q2oL) and Angioedema Quality of Life (AE-QoL). Moreover, in order to collect quality, real-life data on CU patient characteristics, the course of disease, underlying causes, comorbidities, treatment responses, quality of life impairment and health care costs the Chronic Urticaria Registry was recently set up [10].

1.3 Patient-reported outcome measures in Chronic Urticaria

Patient-reported outcome measures are instruments of objective and subjective evaluation for the management of CU and are essential tools for assessing treatment effects in clinical trials.

As described above, CU-Q2oL and AE-QoL are the two questionnaires available for evaluating the CU burden on QoL. Instead, the Urticaria Control Test (UCT) is a valid and reliable tool to assess disease control in patients with CU and a score of ≥12 indicates well-controlled urticaria [1]. However, the most frequently utilized tool in clinical trials is the 7 days Urticaria Activity Score (UAS7) [1, 11]. It is also suitable for evaluation of disease activity by urticaria patients and their treating physicians. The UAS7 is based on the patient self-assessment of the two main urticaria signs and symptoms recorded once a day for 7 consecutive days:

- wheals: 0 = none; 1 = mild (<20 wheals/24 hours); 2 = moderate (20–50 wheals/24 hours); 3 = intense (>50 wheals/24 hours or large confluent areas of wheals);

- pruritus: 0 = none; 1 = mild (present but not annoying or troublesome); 2 = moderate (troublesome but does not interfere with normal daily activity or sleep); 3 = severe (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep).

The sum of score is 0–6 for each day, and 0–42 for the UAS7 (0 = urticaria-free; 1–6 = well-controlled urticaria; 7–15 = mild activity; 16–27 = moderate activity; 28–42 = severe activity), respectively. Overall disease activity is best measured by advising patients to document 24-hour self-evaluation scores for several days.

For the patients affected by recurrent angioedema, alone or in addition to wheals, the last EAACI/GA^{2}LEN/EDF/WAO guideline also suggests to use the Angioedema Activity Score (AAS) [1]. It consists of five items regarding the characteristics of angioedema to have occurred in previous 24 hours [11]. A score between 0 and 3 is assigned to every answer field. The question scores are added up to produce a daily score (0–15). Daily AAS can be summed to give 7-day (0–105), 4-week (0–420), and 12-week scores (0–1260) [12].

1.4 The Chronic Urticaria treatment guidelines

As first-line symptomatic treatment for urticaria, the EAACI/GA^{2}LEN/EDF/WAO guideline suggests regular administration of second-generation, nonsedating, nonimpairing H1-receptor antihistamines due to their efficacy and good safety profile [1]. This class of drugs has a greater receptor specificity, lower penetration of the blood–brain barrier, and less likely to cause drowsiness or psychomotor impairment in comparison to the first-generation antihistamines.

In non-responders adult or paediatric patients, the second-line treatment is the up-dosing of the antihistamine by as much as 4-fold. For patients (aged 12 years and older) who have not responded to four-times the standard dose of second-generation H1-receptor antihistamine, omalizumab, a humanised monoclonal anti-IgE antibody, as add-on therapy is considered the third-line treatment. If there is no response to the omalizumab within 6 months, or if the condition is intolerable, the fourth-line treatment is the prescription of cyclosporine A (CsA), which inhibits the production of IL-2, IL-3, IL-4, and TNF-α in lymphocytes and the IgE-mediated release of histamine from mast cells. High doses of CsA and long duration treatment are associated with adverse events such as abdominal pain, nausea, vomiting, paresthesia, headache, hirsutism, elevated serum creatinine, and hypertension;

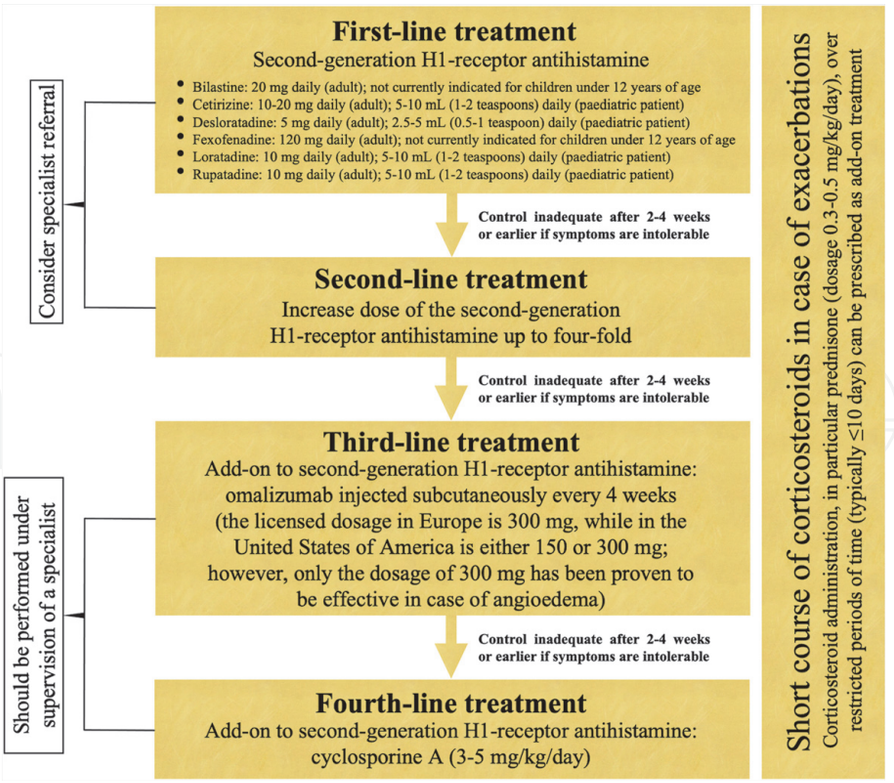

Figure 2.
Simplified stepwise algorithm for the treatment of urticaria adapted from the current EAACI/GA²LEN/EDF/WAO guideline.

however, these side effects resolve after reducing dosage [13]. Nevertheless, CsA should be avoided in patients with chronic kidney disease or poorly controlled hypertension. CsA at the dose of 3–5 mg/kg/day has been shown in small, double-blind, randomised controlled trials to be effective in patients with CSU who do not adequately respond to antihistamines [14, 15]. During CsA treatment, given the significant side effects, the blood pressure, renal function, and serum CsA levels should be monitored regularly.

A simplified stepwise algorithm for the treatment of CSU adapted from the EAACI/GA²LEN/EDF/WAO guideline is summarised in **Figure 2**. At any moment, short courses of corticosteroids (e.g. prednisone 25 mg/daily) are admitted if symptoms are exacerbated or poorly controlled [1].

1.5 The anthystamines limit in Chronic Spontaneous Urticaria

In the pre-omalizumab period, treating CSU patients was a real challenge for physicians due to the low rates of response to H1-antihistamines, which were the only approved medication and the mainstay of symptomatic treatment. Two meta-analysis including studies published between January 1990 and November 2014 revealed that 63.2% and 38.6% of patients remain symptomatic despite treatment with licensed dose and updosed H1-antihistamines, respectively [16]. Another study reported even lower response rates to standard dosage, with disease control in only 22% of patients [17].

2. The role of anti-IgE antibodies in Urticaria

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by foreign invaders such as bacteria, viruses,

parasites, and fungi [18]. The host uses both innate and adaptive mechanisms to detect and eliminate pathogenic microbes, and both of these mechanisms include self-nonself discrimination. Immunoglobulins (Ig), also known as antibodies, are glycoproteins produced by white blood cells that are specific for an antigen (e.g., bacteria, viruses, parasites, or fungi), aiding its destruction by a cascade of downstream pathways. There are five primary classes of Igs (IgG, IgM, IgA, IgD and IgE), which differ in their biological features, structure, target specificity, and distribution [19]. Among them, IgE are involved in allergic reactions with a type I autoimmune mechanism.

2.1 IgE

It is believed that IgE have evolved to protect humans from helminth infections, which are one of the major threats to human life. IgE molecules exist in a monomeric form consisting of two heavy and two light chains and are the most important participants in an allergic reaction [20]. When a foreign substance, called allergen, enters our body, a person with an inherited predisposition to this substance will begin to develop a specific type of IgE, which will evoke a cascade of reactions aimed to eliminating this allergen. IgE are present in serum at very low concentration (∼50–200 ng/mL in a normal individual) and have a very short half-life (1–2 days). However, tissue-resident IgE may persist for several days (approximate half-life of 2 weeks in the skin) [21, 22]. This may be due to the extremely high affinity of IgE for the IgE Fc receptor (FcεRI) and in particular its slow dissociation from this receptor, resulting in re-binding of the dissociated IgE to its receptors, and restricted diffusion away from the tissue within which it resides [23].

There are two structurally and functionally distinct receptors that bind with the Fc epsilon (Fcε) region of IgE: the high affinity FcεRI and the lower affinity CD23 FcεRII [24, 25]. Through their Fc portions, IgE molecules bind to the Fc receptors present on the surface of mast cells and basophils. The cross-linking of such membrane-bound IgE antibodies by multivalent antigens triggers the release of chemically active substances, such as histamine, leukotrienes, prostaglandins, and chemotactic factors, from the cells. These substances initiate allergic and inflammatory reactions and serve as a chemoattractant for other cells [26].

2.2 Anti-IgE antibodies as Chronic Urticaria treatment: why?

This is the first question claimed by the scientific community, since IgE are involved in allergic reactions and CU is not known as an allergic reaction. Before answering this question, we should know the mechanism of action of omalizumab in CSU. Omalizumab has been effective in the treatment of urticaria, believed to have an autoimmune origin, and in cases where the etiology is unknown [27].

There are several hypotheses regarding the mechanism of action of omalizumab in CSU patients. One of them is based on the fact that the density of IgE receptors on the surface of mast cells and basophils is proportional to individual patient's plasma IgE levels [28, 29]. It is hypothesized that omalizumab, by lowering free IgE levels in the blood and subsequently in the skin, may lead to down-regulation of a large percentage of surface IgE receptors, thereby decreasing downstream signaling via the FcεRI receptor pathway [30, 31]. Cell activation would then be diminished, and subsequent inflammatory processes, as complement activation and cellular infiltration, would be suppressed as well. As a consequence, the frequency and severity of symptoms of CSU would be lessened [28, 30, 31].

Another hypothesis is that omalizumab reduces the levels of circulating IgE, leading to a rapid and non-specific desensitization of cutaneous mast cells [32].

Subsequent effects, such as down-regulation of IgE receptor, may help to sustain the response. Serrano-Candelas et al. demonstrated comparable actions of omalizumab on mast cells and basophils while investigating the in vitro mechanism of action of omalizumab on these cells [33].

In a review by Kaplan et al. new insights into the potential mechanisms of action contributing to the efficacy of omalizumab in CIndU/CSU have been suggested based on both clinical and in vitro studies [30]:

- omalizumab lowers IgE levels and down-regulates IgE receptors;
- reduces mast-cell releasability;
- decreases available FcεRI more slowly on mast cells than on basophils;
- reduces IgE+/FcεRI+ cells by ∼12 weeks;
- reverses basopenia and improves basophil IgE receptor function;
- reduces the activity of intrinsically "abnormal" IgE;
- decreases the activity of IgG autoantibodies against FcεRI and IgE;
- reduces the activity of IgE autoantibodies against an antigen or autoantigen that has yet to be definitively identified;
- decreases in vitro coagulation abnormalities associated with disease activity.

Deza et al. investigated the effect of omalizumab on the basophil expression of FcεRI receptor in a cohort of patients with active CSU [34]. Patients exhibiting significant clinical improvement showed a sharp reduction in the levels of basophil FcεRI after 4 weeks ($p < 0.0001$), which was maintained throughout the total duration of the treatment.

In a study by Asero et al., omalizumab responders showed a dramatic decrease of D-dimer plasma levels after the first administration of the drug ($p = 0.003$), suggesting a possible effect of omalizumab on coagulation activation and fibrin degradation [32].

However, none of these theories fully account for the pattern of symptom improvement seen with omalizumab therapy. Therefore, additional research is warranted to further explain the involvement of omalizumab in relieving symptoms associated with the complex, multifactorial pathogenesis of CIndU/CSU.

2.3 The Chronic Spontaneous Urticaria main endotypes

CSU is a mast cell-driven disease. The initial event in the development of skin changes, such as sensory nerve stimulation, vasodilation and extravasation, as well as the recruitment of basophils, eosinophils, and T cells, which lead to whealing, itch, and angioedema is attributed to the degranulation of skin mast cells.

Two groups of mast cell degranulation signals have been so far identified and characterized in CSU pathogenesis: IgE autoantibodies to autoallergens and IgG autoantibodies that target activating mast cell receptors [30]. Therefore, it is now clear that there are at least 2 distinct pathways, type I and type IIb autoimmunity, that contribute to the pathogenesis of this complex disease [35]. In type I hypersensitivity to self, also called autoallergy, antigens crosslink the IgE on mast cells

and basophils to cause release of vasoactive mediators, while in type IIb hypersensitivity antibodies, usually IgG, bind to antigen on a target cell.

About twenty years ago, the demonstration of IgE autoantibodies against the thyroid microsomal antigen thyroperoxidase in the serum of a CSU patient, identified a possible role of type I autoimmunity in the pathogenesis of urticaria [36]. Many studies have further characterized the prevalence and pathogenic relevance of type I autoimmunity in CSU. In particular, CSU patients were found to express more than 2-fold higher IgE-anti-thyroperoxidase serum levels as compared to healthy control subjects ($p < 0.001$) [37].

Kolkhir et al. systematically evaluated the literature on the prevalence of thyroid autoimmunity in CSU and vice-versa, finding a positive correlation between CSU and elevated levels of IgG antithyroid autoantibodies with the studies reporting rates consisted in 10% [38]. Levels of IgG against thyroid peroxidase resulted more often elevated in CSU than those of other IgG antithyroid autoantibodies (strong evidence). Moreover, CSU patients exhibited significantly higher levels of IgG antithyroid autoantibodies (strong evidence) and IgE anti-thyroperoxidase (weak evidence) than controls.

However, IgE autoantibodies directed to a large assortment of autoantigens beyond thyroperoxidase are expressed in the skin of CSU patients as thyroglobulin, tissue factor, and interleukin (IL)-24 [39, 40]. Hatada et al. found that the anti-dsDNA IgE levels were significantly higher in patients with CU than in normal subjects, while no differences in the anti-dsDNA IgG levels were observed [41]. Furthermore, most of the studies confirm that IgE autoantibodies should be responsible for the increased total IgE levels in CSU patients in which, differently to the control subjects, most of the IgE was found to be directed against autoantibodies.

A type IIb hypersensitivity mechanism in which IgG autoantibodies against IgE were involved, was first described in CSU in 1988 [42]. Few years later, IgG autoantibodies directed to FcεRI, the high-affinity receptor for IgE on masthocytes and basophils, were also identified [42]. Grattan et al. introduced the Autologous Serum Skin Test (ASST) in CSU patients, consisting in eliciting with an intradermal injection of their own serum a wheal and flare response [43]. A positive reaction in the ASST confirm the presence of these autoantibodies.

CSU driving by type IIb autoimmune mechanisms is further supported by the basophil activation test [44]. The serum of a subpopulation of CSU patients stimulates heterologous basophils and this activity is due to the presence of autoantibodies against FcεRI as well as in positive ASST responses.

The two endotypes play a key role in inducing different phenotipe of the same disease: type I (autoreactive) and type IIb (autoimmune) CSU patients differ in some features, laboratory markers, and rates and speed of response to treatment [45]. In particular, type IIb autoimmune CSU patients have been suggested to have higher disease activity and longer disease duration as well as higher rates of autoimmune comorbidity. Basopenia and eosinopenia may also be more common.

A higher proportion of patients receiving omalizumab 300 mg achieved response as early as week 4 (early responders) when compared with placebo [46]. This is in line with type I autoimmune/autoreactive mechanism: anti-IgE rapidly binds free IgE, including IgE against autoantigens, and IgE/anti-IgE complexes bind autoallergens preventing mast cell degranulation. CSU patients that take more than a month (late responders) to respond to omalizumab, probably underwent a type IIb autoimmunity, where the reduction of free IgE results in the slow loss of membrane-bound FcεRI from skin mast cells [46].

New endotypes of CSU have been proposed in addiction by recent reports, suggesting a key role of the coagulation pathway factors, ligands of the Mas-related

G protein–coupled receptor X2, basophils, and other signals in the pathogenesis of CSU [47, 48]. Moreover, other research to characterize better the role and the relevance of type I and type IIb autoimmunity in CSU and to support the existence of distinct and separate endotypes, are still in progress.

In contrast to CSU, autoimmunity in CIndU has not yet been described.

3. Omalizumab in Urticaria

Omalizumab is a recombinant deoxyribonucleic acid-derived humanized monoclonal antibody manufactured from a mammalian cell line, that selectively binds to IgE. The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to free IgE, preventing its interaction with FcεRI (**Table 1**). It has been firstly indicated for adults and children (6 years of age and above) with moderate to severe persistent allergic asthma. Ten years later, omalizumab has been approved for the treatment of adults and adolescents (12 years of age and above) with CSU refractory to standard of care.

3.1 Phase II and III clinical studies

Omalizumab preliminary dose selection was provided by the phase II study MYSTIQUE, which evaluated the effect of the drug at different dosages [49]. While these results provided the preliminary data, pivotal dose selection was ultimately evaluated in two pivotal phase III efficacy trials (ASTERIA I and ASTERIA II) and was supplemented by data from the safety trial (GLACIAL) [12]. The GLACIAL study was adequately designed and controlled to provide efficacy information as well.

The MYSTIQUE study assessed the efficacy of three doses of omalizumab (75 mg, 300 mg, and 600 mg) as a single subcutaneous injection in patients with CSU refractory to H1-antihistamines (n = 90), which was followed by a 12-week observation period [49]. The primary endpoint was the mean change in UAS7 at Week 4. Patients in the omalizumab 300 mg and 600 mg groups had significantly greater improvements from baseline in the scores of UAS7 and weekly Itch Severity Score (ISS) compared with those in the placebo group. No additional benefits were observed in the 600 mg group over the 300 mg group. UAS7 scores with omalizumab 75 mg showed only marginal differences versus placebo [50]. The most frequently reported (≥5%) treatment-emergent adverse effects (AEs) during the treatment period were upper respiratory tract infection, headache, nasopharyngitis, and dysmenorrhea. Most AEs were mild to moderate in severity and were considered not related to the study drug [49].

In the XCUISITE study, omalizumab was administered according to the dosing table for allergic asthma using baseline IgE level and weight [50]. Treatment effects were analyzed by individual dose levels for the primary endpoint (change from baseline in UAS7 after 24 weeks) [51]. In the groups receiving omalizumab 300 mg and 150 mg every 4 weeks, a considerable improvement was observed in the UAS7 score compared with that in the placebo group, with a more pronounced effect observed with 300 mg [12]. Although the results of the study suggested a dose–response relationship, no conclusions were made regarding the comparative efficacy between the dose levels since the number of patients in each group was small (n = 6–7) and participants were not randomly assigned to the different dose levels [52]. In terms of safety in the XCUISITE study, the overall incidence of AEs during the treatment period was similar between the omalizumab and placebo groups. The

Anti-IgE Antibodies	Monoclonal antibody type	Equilibrium dissociation constant (K_D)	Pharmacokinetics	Mechanism of action	Administration	Adverse events (most frequent)
Omalizumab, Xolair® (E25, IGE025)	Humanized IgG1/κ-light chain	7×10^{-9} M	• Maximum serum concentration within 7–8 days • Terminal elimination half-life ≈24 days • Steady state serum concentration at week 12	• Attaches to the Cε3 domain of serum IgE, and thereby inhibits these IgE antibodies from binding to FcεRI high-affinity IgE receptor and CD23 receptor • No binding to receptor-bound IgE • Dissociates IgE from FcεRI	• 300 mg (two pre-filled syringes with 150 mg) subcutaneously • Every 4 weeks • Self-administration possible after four tolerated doses	• Injection-site reactions • Upper respiratory infection • Headache
Ligelizumab (QGE031)	Humanized, IgG1/κ-light chain	1.4×10^{-10} M	• Maximum serum concentration within 4 days • Terminal elimination half-life ≈20–25 days • Steady state serum concentration at week 8–16	• Inhibits IgE antibodies from binding to the FcεRI high-affinity IgE receptor • Interference with CD23 binding is debated • No binding to receptor-bound IgE, therefore no triggering of effector cells such as mast cells or basophils	• 120 mg / 240 mg subcutaneously • Every 4 weeks • Final dosing regimen has yet to be defined	• Injection-site reactions • Upper respiratory infection • Headache
UB-221	Humanized IgG1	Not published	Not published	• Attaches to the Cε3 domain of serum IgE, and thereby inhibits these IgE antibodies from binding to FcεRI high-affinity IgE receptor • No inhibition of the interaction between IgE and CD23 • No binding to FcεRI-bound IgE, but binding to CD23-bound IgE, down-regulates IgE synthesis	• 0.2 / 0.6 / 2 / 6 / 10 mg/kg intravenously • Single dose • Final dosing regimen has yet to be defined	Not published
Quilizumab	Humanized, afucosylated, IgG1/κ-light chain	Not published	• Mean maximum observed serum concentrations of 34 ± 12.6 μg/mL at time of maximum observed serum concentration of 36.2 ± 3.5 days • Terminal elimination half-life ≈19–21 days	• Binds membrane IgE at the M1-prime segment • No binding to free IgE	• 300 mg subcutaneously • Every 4 weeks	• Injection-site reactions • Arthralgia • Headache

Table 1.
Summary of the Anti-IgE Antibodies in Chronic Urticaria.

most frequent AEs (>5%) in both groups were diarrhea, nasopharyngitis, and headache. No severe AEs or deaths related to omalizumab were reported [51].

The ASTERIA I, ASTERIA II, and GLACIAL studies were part of the omalizumab registration program in CSU. These were phase III, randomized, multicenter, double-blind, placebo-controlled studies that evaluated the efficacy and safety of omalizumab in patients with CSU [52–54]. Patients with CSU who remained symptomatic despite H1-antihistamine therapy were randomized to receive either placebo or subcutis omalizumab at the dosage of 75 mg, 150 mg, or 300 mg every 4 weeks for a total of 24 weeks in ASTERIA I (n = 319) and 12 weeks in ASTERIA II (n = 323) [52, 53]. The primary endpoint in both trials was the mean change in the ISS score at Week 12. Secondary was to evaluate the variation from baseline to Week 12 in the UAS7 score, weekly number of hives score, median time to minimally important difference in the ISS, weekly size of the largest hive score, proportion of patients with UAS7 ≤ 6, change in the Dermatology Life Quality Index score, proportion of patients with UAS7 = 0, and proportion of angioedema-free days from Week 4 to Week 12.

Instead, GLACIAL (n = 336) primarily evaluated the safety of omalizumab in patients with CSU who remained symptomatic despite treatment with H1-antihistamines (at up to four times the approved dose) plus H2-antihistamines and/or leukotriene receptor antagonists [51], according to the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline at that time [1]. In this study, patients were randomized 3:1 to receive either subcutaneous omalizumab 300 mg every 4 weeks or placebo for 24 weeks.

In all three studies, the treatment period was followed by a 16-week observation period during which no treatment was given [52]. Overall, no new safety issues were identified in the CSU clinical program [51]. No deaths occurred during either trial. The pivotal efficacy trials demonstrated a consistent dose-dependent treatment effect for the evaluated endpoints [49].

Anyway the licensed dosage for omalizumab for refractory CSU, with or without angioedema, in Europe is 300 mg every 4 weeks, independent of patient body weight, body mass index or serum IgE level, while in the USA this is either 150 or 300 mg [12, 52]. Instead, only the dosage of 300 mg every 4 weeks has been proven to be effective in case of angioedema. Currently, the licensed dosage in Italy is 300 mg every 4 weeks over a 6-month period, and in the case of disease recurrence, a minimum of 8 weeks suspension from omalizumab is mandatory, and then it can be prescribed again for a further 5 months only [12]. This schedule (6 months treatment, 8 weeks suspension, and 5 months therapy) can be repeated for eventual relapses; however, this de novo treatment is considered off-label.

To date, there are no licensed treatment options for CIndU and the recommended dosage with omalizumab is similar to CSU.

3.2 Omalizumab: real-life evidences

In clinical settings, the treatment of refractory CSU with omalizumab has been shown to be similar to, or in some cases even better than, those reported by the pivotal randomized controlled trials [12, 55–61].

The retrospective analysis of the three pivotal studies (ASTERIA I, ASTERIA II, and GLACIAL) put first in evidence that some CSU patients respond to treatment more quickly than others and for this reason two different categories were identified: “fast responders” for those who respond within 4–6 weeks and “slow responders” for whom obtain a response more gradually (from 12 to 16 weeks) [12]. However, “slow responders” may still respond even after 24 weeks, while some “fast responders” may obtain a response to treatment within 1 week, suggesting that

the response patterns of patients to omalizumab may be due to the different pathomechanisms of the disease. These two different patterns of response have been soon confirmed by real-life experiences [12, 61–63]. In addition, the clinical assessment of CSU activity was not always uniform in all studies and different patient-reported outcome measures are used, either alone or in combination, to assess disease activity and guide the assessment of treatment efficacy.

Real-world studies have shown a response to treatment in 48–80% cases, while 7–14% are non-responders and 8–50% relapse after drug discontinuation [12, 55–61], supporting the efficacy and safety of omalizumab in CSU patients with an inadequate response to H1-antihistamines. These studies add precious information for the clinical management of CSU, but often present a relatively small sample size population and sometimes include different doses and administration timing of omalizumab. In particular, real-world studies demonstrated that omalizumab administration reduces the use of other CIndU/CSU-related medications. A recent large real-world retrospective study including 1546 patients with CIndU/CSU treated with omalizumab revealed that the majority started with a dosage of 300 mg and received the drug for an average of 9 months without dosing titration up or down [64]. Moreover, the use of other medications, such as corticosteroids and antidepressants, was consistently decreasing during the follow-up period, from 72.8% over the first 3 months to 58.5% over the last 3 months.

Additionally, real-life experiences have confirmed that there are different patient profiles according to omalizumab response [63, 65, 66]:

- patients typically show a response to treatment within the first 4–8 weeks (often within 1 week);

- patients initially non-responders can obtain a significant reduction in disease activity and even achieve "good control" (UAS7 $\leq$ 6) or "complete control" (UAS7 = 0) if the treatment is continued for up to 24 weeks.

Other different strategies mainly involve either modification of the omalizumab dose or a change in the treatment interval. Dose increases or reductions, if the complete CU symptoms control is achieved, should be stepwise [63].

Data on the response rate to omalizumab is available from meta-analyses and real-world evidence, but not all of them have assessed the time to response and, due to the different dosages and treatment durations, it is difficult to draw a common conclusion from these studies [32, 46, 49, 50, 53, 56, 57, 66–74]. Consequently, several parameters have been suggested to potentially predict treatment response, or possible treatment relapse. Some studies have been focused on different baseline clinical and laboratory parameters in order to identify the predictors of response to omalizumab in CSU patients. Asero et al. found that high levels of D-dimer seems to be a marker of response to treatment [32], but more recently the same authors and other studies indicate D-dimer only as a activity/severity marker in CSU patients and its plasma levels are reduced by omalizumab both in patients with and without angioedema at baseline [75]. Instead, many studies have shown that total IgE levels can be a marker of response to omalizumab [76]. Marzano et al. recently confirmed IgE basal levels as a reliable biomarker predicting response to treatment in CSU patients, while they did not support the usefulness of D-dimer [62]. In a single-center study on 47 CSU patients the baseline basophil FcεRI expression was found to be a potential immunological predictor of good and fast response to omalizumab (100% sensitivity and 73.2% specificity) [34].

The analysis of omalizumab responders in a prospective study of 64 patients showed that most basophil histamine release assay (BHRA)-positive patients

responded only after the second injection, with a median time to response of 29 days, whereas BHRA-negative patients had a median time to response of only 2 days [77].

In a retrospective study of 41 antihistamine-refractory CU patients, the lack of basophil CD203c-upregulating activity in their serum correlated negatively with a clinical respond to omalizumab [78]. In detail, a significant association was found between the response and CD203c-upregulating activity, autoimmune phenotype, low IgE levels, and high eosinophil count levels.

Greater number of prior medications was associated with a lack of response to omalizumab in a study of 52 patients with severe CU, whereas the presence of anaphylaxis, angioedema, dermatographism, steroid use, and disease duration were not [79].

Furthermore, CSU duration before omalizumab and baseline UAS7 may be considered a negative markers of response and high relapse risk [62]. Although the response to omalizumab should not be dose dependent in CSU, real-life settings have shown that body mass index could influence the performance of the drug [17].

In a cohort of 154 patients the following factors were described as possible predictors of a favourable response to omalizumab [80]:

- diagnosis of CSU vs. CIndU;
- no prior treatment with immunosuppressant drugs;
- older age;
- shorter duration of symptoms;
- absence of angioedema;
- negative histamine release test.

Over 85% of patients who present these characteristics achieved a complete respond to treatment.

In relation to the dosing, the proportion of patients who showed complete response to omalizumab 150 mg ranged from 15–22% in clinical trials and from 36–79% in real-world studies. Regarding omalizumab 300 mg, the proportion of complete responders ranged from 34–44% in clinical trials and from 40% to 84.6% in real-life settings. However, not all real-world studies provided information on treatment duration. In few real-world studies where patients have received either/both omalizumab 150 mg and 300 mg, the complete response was observed in 47–83%. In addition, a complete response was achieved as early as the day after the administration of the first dose or within 5 months [66–74].

Real-world settings support that repeated treatment cycles should be required in several CSU patients [12, 70, 74, 81, 82]. Regarding the retreatment, omalizumab seems to be highly efficient in relapsed patients who previously had responded well [74]. An Italian retrospective clinical analysis revealed that the second cycle treatment with omalizumab is effective more quickly compared to the first cycle response [12]. Based on current international guidelines, omalizumab labelling information and experience in clinical practice, an Italian group provided treatment recommendations regarding the use of omalizumab in patients with CSU concluding that repeated cycles or extended treatment may be necessary in patients with disease relapse or late treatment response [81]. These authors suggested to continue the treatment when patients have a UAS7 > 6 and/or UCT < 12.

Among responders, after discontinuation of omalizumab the treatment can be resumed at a later stage with the same degree of symptom control [82].

All the real-world studies underlined the high safety prophile of omalizumab also in continuous and long-term administration. Finally, in a meta-analysis of 67 published reports, benefits and safety of omalizumab in the real-world treatment of CSU have met or exceeded results achieved in clinical trials [83].

3.3 Omalizumab performances optimization in clinical practice

Current evidence indicates that CSU usually last from 3 to 12 months, but patients may be affected for more than 1 year (sometimes even more than 5 years) [84]. However, recommendations regarding treatment duration and re-treatment after symptoms return are lacking. Nevertheless, the primary results of the OPTIMA study have shown that approximately 88% of patients who relapsed after being previously well-controlled with omalizumab, regain symptom control upon re-treatment within 3 months [85]. Similarly, phase IV XTEND-CIU study and few real-world studies have shown re-treatment to be effective in CSU patients who had previously responded to omalizumab but who relapsed after treatment withdrawal [4, 86]. To date, there are limited data comparing the therapeutic effect of omalizumab for patients with CSU, CIndU, and CSU plus CIndU. A recent chinese study revealed that omalizumab is highly effective and safe in 138 patients with difficult-to-treat CSU, CIndU, or both [87]. Among the CU patients enrolled, 87% responded to omalizumab therapy and those with higher baseline total IgE levels and longer disease durations showed more likely to experience rapid relapse after discontinuation of the drug.

Many other important questions regarding the use of omalizumab remain to be answered in order to optimize treatment management and patient outcomes. In particular, further investigations regarding predictors of good outcome, optimal dose, and dosing intervals based on treatment response to omalizumab in CSU are needed. A personalized therapeutic algorithm according to the patient clinical and bio-markers, modulated on the dose–response pattern, should facilitate the clinical management of omalizumab and help clinicians to determine the most appropriate therapeutic strategy for CSU. Future research is, therefore, required to evaluate the role of omalizumab in the various subtypes of CU as well as to establish standardized protocols for dosing and monitoring adverse effects of long-term therapy.

4. Ligelizumab (QGE031)

Even though omalizumab has been changing the management of CU, there is still a need for new targets and new biologics targeting new pathways in the management of the disease, which should provide long-lasting remission, be administered orally and cheaper. Among the CSU treatments that are still under clinical trials, there is anothers anti-IgE drug called ligelizumab (QGE031), which has been developed with the intention of overcoming some of the limitations associated with omalizumab [88].

4.1 Ligelizumab: what is it and how does it work in Chronic Spontaneous Urticaria

Ligelizumab, a next-generation high-affinity fully human monoclonal IgG anti-IgE antibody, demonstrated dose- and time-dependent suppression of free IgE, basophil FcεRI and basophil surface IgE superior in extent (free IgE and surface

IgE) and duration to omalizumab (**Table 1**) [89, 90]. Ligelizumab recognizes a distinct IgE epitope only partially overlapping with that of omalizumab, interacting across the IgE-Fc dimer and favors the recognition of IgE in an open conformation different from its FcεRI- or CD23-bound conformations. Moreover, it binds IgE with significantly higher affinity (almost 50-fold higher) than omalizumab and shows a correspondingly enhanced inhibition of IgE binding to FcεRI and basophil activation. However, ligelizumab is inferior to omalizumab in preventing IgE binding to CD23. Structural analysis indicates that differences in the ligelizumab epitope and spatial orientation on IgE contribute to this differential inhibition [91].

Indeed, ligelizumab and omalizumab recognize distinct binding epitopes in the IgE Cε3 domain, showing some overlap but also different sensitivities to IgE conformation. On one side, the increased affinity of ligelizumab for IgE is superior than omalizumab regarding neutralization of free serum IgE, on the other side the additional mode of action for ligelizumab through the inhibition of IgE production may provide additional therapeutic benefit. Indeed, ligelizumab is more efficient in suppressing FcεRI-dependent allergic reactions in an in vivo model, while omalizumab may have advantages in blocking antigen presentation and transport processes that are dependent on IgE:CD23 interactions [92, 93].

4.2 Ligelizumab clinical studies

Currently, ligelizumab is being developed solely for the treatment of CSU. Phase IIb randomized controlled trial (NCT02477332) in CSU (CQGE031C2201) results demonstrated ligelizumab to be efficacious at 72 mg and 240 mg dosage, showing superiority over omalizumab and a comparable good safety profile [94]. The subsequent extension study (NCT02649218) in CSU (CQGE031C2201E1) proved the efficacy and safety of the ligelizumab at the dose of 240 mg every 4 weeks for a 1-year period, achiving more prolonged symptom control compared to the core study [95, 96].

4.2.1 CQGE031C2201

This was a 20-weeks multi-center, randomized, double-blind, placebo- and active controlled phase IIb dose-range finding study in subjects with CSU inadequately controlled [94]. CSU patients included in the study had to have a moderate-to-severe CSU defined as UAS7 of at least 16, 7 days hives severity score (HSS7) of at least 8, and in-clinic UAS of at least 4 (range 1 to 6) on at least one of the screening visit days. Exclusion criteria were represented by a previous exposure to omalizumab or ligelizumab, any other skin disease that is associated with chronic itching that might confound the trial evaluations and results, and a clearly defined underlying cause of CU other than CSU (e.g., inducible urticaria).

Subjects were randomized into 1 of 6 parallel treatment arms at a ratio of 1:2:2:2:1:1 (subcutaneous injections every 4 weeks of ligelizumab 24 mg, 72 mg, or 240 mg, omalizumab at a dose of 300 mg, a single dose of ligelizumab 120 mg followed by placebo or placebo) for the 20-week treatment period. The single 120 mg dose of ligelizumab was used to gain blinded wash-out information in relation to return of symptoms.

During the screening, treatment, and follow-up periods, nonsedating H1-antihistamines were used as rescue medication. Moreover, as background medication, this trial required concurrent use of H1-antihistamines at locally approved doses or at increased doses up to four times alone or in combination with H2-antihistamines or leukotriene-receptor antagonists (montelukast, zafirlukast, or pranlukast), according to the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline at that time [1].

Primary end-point was the achievement of complete hives response (HSS7 = 0) at week 12 (four weeks after the last injection), similar to phase III trials of omalizumab. Among 574 patients screened, 382 were included and 338 completed the treatment phase. The mean age ± SD of the study population was 43.3 ± 12.5 years (range 18 to 75 years) and 75% of subjects were female. Mean time since diagnosis of CSU was 4.3 ± 6.0 years. Median IgE levels at baseline was 87.2 IU/ml (range 0 to 14100).

With ligelizumab the main objective of the trial was achieved, showing a dose–response relationship with respect to the achievement of a HSS7 of 0 at week 12. The relationship resulted in a plateau starting close to the 72 mg dose of ligelizumab, while no further improvement in response was noted with the dosage of 240 mg.

At week 12, complete hive response was achieved in 30%, 51%, and 42% of patients treated with 24 mg, 72 mg, and 240 mg ligelizumab, respectively. Instead, a HSS7 of 0 was achieved only in 26% of patients with omalizumab and in none of those in the placebo group. The 7 days itch severity score (ISS7) showed a pattern similar to that seen with the hives-severity score. At week 12, UAS7 of 0 was achieved in 30%, 44%, and 40% of patients treated with ligelizumab 24 mg, 72 mg, and 240 mg, respectively, in comparison to 26% with omalizumab and none with placebo. Considering the scores (ISS7, UAS7, and HSS7) achieved, ligelizumab demonstrated superiority not only over placebo but also over omalizumab. In addition to hives and itch the AAS decreased to −21.1, −37.6, and − 27.3 among patients treated with 24 mg, 72 mg, and 240 mg ligelizumab, respectively, in comparison to −23.1 in patients with omalizumab and − 23.6 in the placebo group.

At week 4, the effect of the single 120 mg ligelizumab dose was similar to that seen with 72 mg and 240 mg and lasted until week 8. In contrast, a partial relapse of symptoms was noted with the 72 mg ligelizumab toward the end of the administration interval of four weeks. These data gave evidence that a dose higher than 72 mg ligelizumab could potentially provide enough drug effect throughout the administration interval of four weeks, minimizing symptom relapse. In support of this sustained treatment effect, the median time to loss of complete response in patients who had an UAS7 of 0 at the end of the treatment (week 20) was greatest in the patients treated with 240 mg of ligelizumab (10.5 weeks), while was similar in the groups that received 72 mg of ligelizumab or 300 mg of omalizumab (4 weeks).

Similar to omalizumab, the most frequent AEs were mild to moderate injection site reactions after subcutaneous administration (4% and 7% of patients treated with the 72 mg and 240 mg, respectively). All other minor AEs (mainly upper respiratory infections and headaches) showed no meaningful difference among the trial groups. Deaths, anaphylaxis or serious adverse events to ligelizumab have not been reported.

4.2.2 CQGE031C2201E1

Patients who completed CQGE031C2201 were eligible to be enrolled in this extension study at week 32 that confirmed the safety of the long-term (52 weeks) administration of the highest dose of ligelizumab (subcutaneous injections every 4 weeks of ligelizumab 240 mg) [95]. At week 52, 61.1% of patients achieved UAS7 ≤ 6 and, after stopping treatment, the median time of well-controlled disease was 28.0 weeks. These results implicate a longer treatment effect of ligelizumab compared to omalizumab [96].

4.2.3 CQGE031C1301

CQGE031C1301 represents a phase II multi-center, open-label study (NCT03907878) to investigate the safety/tolerability and efficacy of ligelizumab

120 mg every 4 weeks in adult Japanese patients with CSU inadequately controlled with H1-antihistamines. Currently, CQGE031C1301 is still ongoing.

4.2.4 Phase III ligelizumab study

Currently, two similar trials (PEARL 1 NCT03580356 and PEARL 2 NCT03580369) are ongoing to study the efficacy and safety of ligelizumab (72 mg or 120 mg every 4 weeks) in CSU patients who remain symptomatic despite standard of care treatment [97]. Both are 52-weeks multi-center, randomized, double-blind, placebo- and active controlled phase III trials and is planned to enroll about 1000 patients for each study.

In addition, a phase IIIb extension study is planned to investigate ligelizumab in adult and adolescent patients with CSU (NCT04210843) [98].

Results from these studies may confirm whether ligelizumab should become an alternative first-line treatment option in H1-antihistamine refractory CSU patients.

5. Anti-IgE antibodies in Chronic Spontaneous Urticaria special populations and drug interactions

To date, ligelizumab have not been investigated pregnant women, children, elderly, history of cancer, patients with renal or hepatic impairment, while only few studies were published regarding the use omalizumab in these special populations.

5.1 Pregnancy

Currently, omalizumab is not approved for use in pregnancy and there are only few case reports published in literature describing omalizumab as an effective and safe therapy for urticaria in pregnant women [99–102].

The EXPECT study examined 250 women with with moderate-to-severe asthma exposed to omalizumab during pregnancy [102]. Each enrolled patient received at least one dose of omalizumab during pregnancy up to 8 weeks prior to conception. This study compared EXPECT outcomes with those from a disease-matched external population of pregnant women with moderate-to-severe asthma not treated with omalizumab. No significant difference in spontaneous abortions, major congenital anomalies, prematurity, or low birth weight was observed among pregnant women exposed to omalizumab compared with the disease-matched unexposed cohort. However, given the observational nature of this registry, an absence of increased risk with omalizumab cannot be definitively established. Therefore, omalizumab might be considered in pregnant women, but to date its use during pregnancy is not recommended by any accepted international or national guideline. Randomized controlled trials should be conducted on omalizumab during pregnancy before complete reassurance of the drug is established.

5.2 Children

Randomized controlled trials using omalizumab in urticaria included only a small number of 39 adolescent patients (aged ≥12 years) [103]. Passanisi et al. reported a case series of six children (66.7% males) with a mean age of 14.7 years (range 11–16 years) treated with at least one 6-months course of omalizumab [103]. The average follow-up period was 13 ± 6 months and only one patient was no responder, while three patients needed a second course of treatment. This study demonstrated that omalizumab is effective and safe as treatment option for CSU

unresponsive adolescent patients. Moreover, Passanisi et al. summarized in his study the 12 previously published case reports. Applied omalizumab doses ranged from 75 mg every 4 weeks to 300 mg every 2 weeks for a period of up to 12 months, but most patients received the standard dose of 300 mg every 4 weeks.

Recently, a retrospective multi-center case series reported the use of omalizumab in 19 children (6 to 16.9 years old) with recalcitrant CSU [104]. Sixteen (84%) responded to omalizumab, although two became non-responsive after 6–12 months of therapy, while three patients (16%) were resistant to treatment, achieving remission through fourth-line (Cyclosporine A) or other therapies. This study stated that children with recalcitrant CSU, even those <12 years old, respond well to standard-dose of omalizumab at rates similar to adults. Future prospective randomized clinical trials of omalizumab and other anti-IgE therapies in children are needed.

5.3 Elderly (65 Years and Older)

Whilst the randomized clinical trials had an upper age limit of 75 years, the mean age of all included CSU patients was within the range of 40–45 years. Therefore, limited data are now available on the use of anti-IgE antibodies in patients older than 65 years, but there is no evidence that elderly patients require a different dose from younger adult patients. A recent Italian real-life experience on 32 patients ≥65 years of age found that omalizumab is a well-tolerated and effective therapy for elderly patients with nonsedating H1-antihistamine-refractory CSU [105].

5.4 History of cancer

To date, there are only few reports of effective and safe omalizumab treatment in patients with a history of previous cancer (e.g. with breast carcinoma, in-situ melanoma, thyroid carcinoma, laryngeal carcinoma, and pituitary adenoma) [106], while evidence in patients with active malignant disease is scarce. Very rarely CU can be caused by cancer and if so, resolves with its cure [107]. Therefore, current expert opinion suggested that omalizumab can be used in patients with cancer [108].

5.5 Patients with renal or hepatic impairment

As IgG monoclonal antibodies are mainly eliminated via intracellular catabolism, renal impairment or hepatic impairment is not expected to influence clearance of ligelizumab and omalizumab. No dedicated drug–drug interaction studies have been conducted so far. Hepatic metabolizing enzymes are not involved in monoclonal antibody elimination, consequentely no pharmacokinetic interactions with co-administered medicinal products are expected with the both medications.

6. The future in Chronic Spontaneous Urticaria: anti-IgE antibodies and beyond

In addition to drug repurposing as in anti-IL-4/13, IL-5, and IL-17 antibodies, novel targeted therapy options are currently undergoing clinical trials and will be available in the near future: other anti-IgE antibodies such as UB-221 and Quilizumab, molecules targeting intracellular signaling pathways such as spleen tyrosine kinase inhibitors, surface inhibitory molecules such as siglec-8, anti-IL-1s such as canakinumab, Bruton kinase inhibitors such as GDC-0853 and anti-IL-5s

such as benralizumab and mepolizumab [5, 109]. New potential target molecules are going to be proposed as novel treatments and have been rapidly developing.

6.1 UB-221

UB-221 is a humanized IgG1 mAb (clone 8D6) that targets the Cε3 domain of IgE antibody and, unlike omalizumab, it can bind to IgE bound by CD23 (**Table 1**). UB-221 neutralizes IgE without activation of mast cells and basophils and was superior to omalizumab while targeting IgE by 3- to 8-folds in terms of pharmacologic effects. It is currently being investigated in two ongoing phase I trials for safety, tolerability, pharmacodynamics, and pharmacokinetics following a single dose (0.2, 0.6, 2, 6, 10 mg/kg UB-221 intravenously vs. placebo) in adult patients with CSU inadequately controlled with H1-antihistamines (NCT03632291 in Taiwan, and NCT04175704, location not provided).

6.2 Quilizumab

Quilizumab is a humanized, afucosylated, monoclonal IgG1 antibody, that binds membrane-bound IgE on B cells at the M1-prime segment, which is absent in soluble IgE (**Table 1**). In healthy volunteers and patients with allergic rhinitis or asthma, this anti-IgE antibody resulted able to reduce the total and specific IgE serum levels for at least 6 months after the last dose [110, 111]. This may implicate that quilizumab affects long-term IgE memory and bears the capacity for a sustained effect compared to omalizumab. Regarding quilizumab, there is no published evidence about its effect on angioedema and only one clinical trial is currently ongoing (NCT01987947) in CU. A previous randomized trial of quilizumab in adults with refractory CSU revealed that, although it reduced median serum IgE levels by approximately 30% over 20 weeks, it did not cause clinically relevant effects as assessed by ISS7 and UAS7 [112]. The study investigators hypothesized that the remaining serum IgE may be produced by long-lived IgE plasma cells that are not targeted by the drug due to their lack of membrane IgE.

6.3 Other possıble targets for treatment

Some other molecules participating in the pathogenesis of CSU might be important targets for treatment in the upcoming years.

- In patients with CSU, C5a has been shown to enhance histamine release from mast cells upon activation of FcεRI through IgG autoantibodies [113]. Moreover, activation with C5a led to an increased basophil response in patients with CU compared to healthy controls [114]. These finding indicate a possible role for C5a in CSU and provide a basis for the evaluation of C5a inhibitors (IFX-1, eculizumab) in the treatment of CSU [115].

- SHIP has been shown to be a key “gatekeeper” of mast cell degranulation. [116]. Indeed, SHIP acts as a negative regulator of degranulation by hydrolyzing phosphatidylinositol-3,4,5-trisphosphate, a second messenger generated in activated cells by phosphatidylinositol 3-kinase. SHIP-negative mast cells are more likely to degranulate following IgE binding. Instead, CD200R represents a novel and potent inhibitory receptor that can be targeted in vivo to regulate mast cell-dependent pathologies [117]. Considering their regulatory functions on mast cells, the use of SHIP and CD200R antibodies might be of interest in CSU.

- Histamine H4 receptors (H4R) are expressed by hematopoietic cells including eosinophils, mast cells, neutrophils, and T cells. Activation of H4 receptors results in chemotaxis, cytokine production, immunomodulation, and inflammatory cell trafficking [118]. The use of H4R-antagonist called JNJ-7777120 has been associated with reduction of histamine-mediated scratching and Th2-induced inflammation in dermatitis [119]. Another H4R-antagonist, ZPL-3893787, improve inflammatory skin lesions in patients with atopic dermatitis compared to placebo [120]. The anti-inflammatory and anti-pruritic effects of H4R-antagonists might be of benefit in CSU treatment.

- IL-31 is a pro-inflammatory cytokine mainly secreted by Th2 cells that exerts its effects through two receptors: IL-31 receptor A and oncostatin M receptor (OSMR) [121]. Increased expression of OSMR protein and histamine release were also shown in chronic autoimmune urticaria. In addition, OSMR gene silencing in mice led to a decrease in inflammatory cytokines and number of eosinophils [122]. These data indicate that IL-31 or OSMRβ inhibitors (e.g., nemolizumab, vixarelimab) might play an interesting role in the treatment of CSU.

- Increased levels of IL-6, another pro-inflammatory cytokine, have been demonstrated in patients with CSU [123]. It was also correlated with disease severity, suggesting the role of systemic inflammation in CSU. Tocilizumab, an IL-6 monoclonal antibody, led to improvement in patients with Schnitzler syndrome, and might be of potential benefit for CSU treatment [124].

- The increased expression of Mas-related gene X2, which is a receptor for histamine-releasing neuropeptides including substance P and vasoactive intestinal peptides, was demonstrated to be a possible therapeutic target in mast cells of patients with CSU [125].

- The antagonists for neurokinin receptor-1 (e.g., aprepitant, tradipitant), which is the main cutaneous receptor for substance P, are under investigation for atopic dermatitis for their antipruritic effects and they might be of value for CSU as well [126].

- The expression of thymic stromal lymphopoietin (TSLP), a promotor of Th2 response, was shown to be increased in patients with CSU, thus making the anti-TSLP monoclonal antibody, tezepelumab, a potential treatment option for CSU [127].

- Calcium Release-Activated Calcium Modulator 1 (CRACM1/ORAI1) is a subtype of Ca2+ membrane channel, causing Ca2+ influx into the cells and mast cell degranulation [128]. Ca2+ is an essential element that regulates immune responses, especially in the development and function of T and B cells, and therefore ORAI1 is considered to participate in allergic diseases. Jie et al. have demonstrated that different single nucleotide polymorphisms in the ORAI1 gene are associated with an increased risk of CSU and better response to desloratadine [129]. Thus, targeting of ORAI1 via silencing RNAs might be of therapeutic value in CSU.

7. Conclusions

The introduction of anti-IgE antibodies in urticaria management has been representing a milestone in the treatment of H1-antihistamine refractory patients.

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
X-CUISITE	II	Chronic spontaneous urticaria° (patients exhibit IgE against thyroperoxidase)	49	• Omalizumab 75 to 375 mg according to baseline IgE and body weight	Not evaluated with score	*Week 24* UAS7 = −17.8 DLQI = −6.3 CU-Q2oL = −21	*Week 24* UAS7 = −7.9 DLQI = −1.5 CU-Q2oL = −2.3	2011 [50]
MYSTIQUE	II	Chronic spontaneous urticaria°	90	• A single dose of omalizumab 75 mg • A single dose of omalizumab 300 mg • A single dose of omalizumab 600 mg	—	*Week 4* • Omalizumab 75 mg UAS7 = −9.8 ISS7 = −4.5 HSS7 = −5.3 • Omalizumab 300 mg UAS7 = −19.9 ISS7 = −9.2 HSS7 = −10.7 • Omalizumab 600 mg UAS7 = −14.6 ISS7 = −6.5 HSS7 = −8.1	*Week 4* UAS7 = −6.9 ISS7 = −3.5 HSS7 = −3.5	2011 [49]
MoA	II	Chronic spontaneous urticaria° (healthy controls included)	40	• Omalizumab 300 mg	AEFD	*Week 4 to 12* AEFD = 90.9 *Week 12* UAS7 = −23.1 CUQ2oL = −39.2 DLQI = −10.2	*Week 4 to 12* AEFD = 70.5 *Week 12* UAS7 = −8.1 CUQ2oL = −5.7 DLQI = −3.1	2019 [130]

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
X-ACT	III	Chronic spontaneous urticaria°	91	• Omalizumab 300 mg	AEBD AE-QoL MAEBD MTFRAE	*Week 0 to 28* AEBD = 14.6 MAEBD = 9 days *Week 28* UAS7 = −16.8 CUQ2oL = −30.9 DLQI = −10.5 AE-QoL = −41.4 MTFRAE = 56–63 days	*Week 0 to 28* AEBD = 49.5 MAEBD = 30 days *Week 28* UAS7 = −6.5 CUQ2oL = −12.1 DLQI = −5.6 AE-QoL = −24.2 MTFRAE = <5 days	2016, 2018 [131, 132]
ASTERIA I	III	Chronic spontaneous urticaria°	319	• Omalizumab 75 mg • Omalizumab 150 mg • Omalizumab 300 mg	AEFD	*Week 4 to 12* • Omalizumab 75 mg AEFD = 86.5 • Omalizumab 150 mg AEFD = 89.6 • Omalizumab 300 mg AEFD = 96.1 *Week 12* • Omalizumab 75 mg UAS7 = −13.8 ISS7 = −6.5 HSS7 = −7.4 DLQI = −6.3 CU-Q2oL = −19.2 • Omalizumab 150 mg UAS7 = −14.4 ISS7 = −6.7 HSS7 = −7.8 DLQI = −8.0 CU-Q2oL = −23.1 • Omalizumab 300 mg UAS7 = −20.8	*Week 4 to 12* AEFD = 88.2 *Week 12* UAS7 = −8.0 ISS7 = −3.6 HSS7 = −4.4 DLQI = −6.1 CU-Q2oL = −19.7 *Week 24* UAS7 = −11.73 ISS7 = −5.4 HSS7 = −6.3 *Week 40 (at the end of 16 weeks of follow-up)* DLQI = −7.9	2015 [54]

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
						ISS7 = −9.4 HSS7 = −11.4 DLQI = −10.3 CU-Q2oL = −30.5 *Week 24* • Omalizumab 75 mg UAS7 = −14.9 ISS7 = −7.0 HSS7 = −8.0 • Omalizumab 150 mg UAS7 = −14.2 ISS7 = −6.5 HSS7 = −7.8 • Omalizumab 300 mg UAS7 = −22.1 ISS7 = −9.8 HSS7 = −12.3 *Week 40 (at the end of 16 weeks of follow-up)* • Omalizumab 75 mg DLQI = −7.0 • Omalizumab 150 mg DLQI = −5.2 • Omalizumab 300 mg DLQI = −4.9		
ASTERIA II	III	Chronic spontaneous urticaria°	323	• Omalizumab 75 mg • Omalizumab 150 mg • Omalizumab 300 mg	AEFD	*Week 4 to 12* • Omalizumab 75 mg AEFD = 93.5 • Omalizumab 150 mg AEFD = 91.6 • Omalizumab 300 mg	*Week 4 to 12* AEFD = 89.2 *Week 12* UAS7 = −10.4 ISS7 = −5.1 HSS7 = −5.2	2013 [52]

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
						AEFD = 95.5 *Week 12* • Omalizumab 75 mg UAS7 = −13.82 ISS7 = −5.9 HSS7 = −7.2 DLQI = −7.5 CU-Q2oL = −20.6 • Omalizumab 150 mg UAS7 = −17.9 ISS7 = −8.1 HSS7 = −9.8 DLQI = −8.3 CU-Q2oL = −27.0 • Omalizumab 300 mg UAS7 = −21.7 ISS7 = −9.8 HSS7 = −12.0 DLQI = −10.2 CU-Q2oL = −31.4	DLQI = −6.1 CU-Q2oL = −17.7	
GLACIAL	III	Chronic spontaneous urticaria*	336	• Omalizumab 300 mg	AEFD	*Week 4 to 12* AEFD = 91.0 *Week 12* UAS7 = −19.0 ISS7 = −8.6 HSS7 = −10.5 DLQI = −9.7 CU-Q2oL = −29.3	*Week 4 to 12* AEFD = 88.1 *Week 12* UAS7 = −8.5 ISS7 = −4.6 HSS7 = −4.5 DLQI = −5.1 CU-Q2oL = −16.3	2013 [53]

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
POLARIS	III	Chronic spontaneous urticaria°	218	• Omalizumab 150 mg • Omalizumab 300 mg	—	*Week 12* • Omalizumab 150 mg UAS7 = −18.8 ISS7 = −8.8 HSS7 = −10.0 DLQI = −7.2 • Omalizumab 300 mg UAS7 = −22.4 ISS7 = −10.2 HSS7 = −12.2 DLQI = −8.4	*Week 12* UAS7 = −13.9 ISS7 = −6.5 HSS7 = −7.4 DLQI = −5.3	2018 [133]
UFO	II	Symptomatic dermographism	61	• Omalizumab 150 mg • Omalizumab 300 mg	—	*Week 10* • Omalizumab 150 mg CFT = −1.8 CR = 44% • Omalizumab 300 mg CFT = −2.0 CR = 53%	*Week 10* CFT = −0.6 CR = 11%	2017 [134]
CUN-OMAL-UCOL	II	Cholinergic urticaria§	22	• Omalizumab 300 mg (first 4 months blinded, followed by 8 months open-label)	—	*Week 16* No difference in negative exercise challenge test rate compared to placebo UCOL score = −28 CU-Q2oL = −7.6 VAS = −10 *Week 48* Negative exercise challenge test: 31% Significant progressive improvement along time starting from week 16	*Week 16* UCOL score = −16 CU-Q2oL = −6.5 VAS = −10 *Week 48* Theoretical negative exercise challenge test: 11%	2019 [135]

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
CUTEX	II	Cold urticaria	31	• Omalizumab 150 mg • Omalizumab 300 mg	—	*Week 10* • Omalizumab 150 mg CTT = −10.6°C CR = 40% • Omalizumab 300 mg CTT = −10.4°C CR = 44%	*Week 10* CTT = −0.3°C CR = 0%	2017 [136]
XOLUS	II	Solar urticaria	10	• Omalizumab 300 mg	—	*Week 12* MUDi = 20% DLQI <6 = 40% VAS50 = 40% *Week 20* MUDi = 0% DLQI <6 = 11% VAS50 = 0%	No placebo arm; comparison to baseline	2016 [137]
CQGE031C2201	IIb	Chronic spontaneous urticaria*	382	• Ligelizumab 24 mg • Ligelizumab 72 mg • Ligelizumab 240 mg • Omalizumab 300 mg	AAS7	*Week 12* • Ligelizumab 24 mg UAS7 = −16.0 ISS7 = −7.0 HSS7 = −9.0 AAS7 = −20.0 • Ligelizumab 72 mg UAS7 = −27.0 ISS7 = −10.3 HSS7 = −16.5 AAS7 = −37.6 • Ligelizumab 240 mg	*Week 12* UAS7 = −13.0 ISS7 = −5.0 HSS7 = −7.5 AAS7 = −23.6 *Week 20* UAS7 = −12.0 ISS7 = −5.5 HSS7 = −6.5 AAS7 = −24.4	2019 [94]

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
						UAS7 = −22.9 ISS7 = −10.0 HSS7 = −14.0 AAS7 = −29.9 • Omalizumab 300 mg UAS7 = −18.5 ISS7 = −8.8 HSS7 = −11.0 AAS7 = −25.0 *Week 20* • Ligelizumab 24 mg UAS7 = −19.5 ISS7 = −7.5 HSS7 = −9.75 AAS7 = −22.6 • Ligelizumab 72 mg UAS7 = −26.5 ISS7 = −9.5 HSS7 = −15.5 AAS7 = −35.2 • Ligelizumab 240 mg UAS7 = −21.8 ISS7 = −9.0 HSS7 = −13.5 AAS7 = −27.3 • Omalizumab 300 mg UAS7 = −19.0 ISS7 = −8.0 HSS7 = −11.0 AAS7 = −23.1		

Name of the Study	Phase	Indication	Patients included	Anti-IgE antibodies dose every 4 weeks	Efficacy on Angioedema	Outcome with anti-IgE antibodies	Outcome with placebo	Year of publication [reference]
QUAIL	IIb	Chronic spontaneous urticaria^	32	• Quilizumab 450 mg	—	*Week 20* UAS7 = −2.0 ISS7 = −5.3 HSS7 = −0	*Week 20* UAS7 = −11.0 ISS7 = −2.2 HSS7 = −3.5	2016 [112]

Abbreviations: *7 days Angioedema Severity Score, AAS7; 7 days Hives-Severity Score, HSS7; 7 days Itch Severity Score, ISS7; 7 days Urticaria Activity Score, UAS7; Angioedema Free Days, AEFD; Angioedema Burdened Days, AEBD; Angioedema Quality of Life, AE-QoL; Cholinergic Urticaria score, UCOL score; Chronic Urticaria Quality of Life, CU-Q2oL; critical friction threshold, CFT; complete response, CR; Dermatology Life Quality Index, DLQI; Median Angioedema Burdened Days, MAEBD; Median Time to First Recurrence of Angioedema after last injection of study drug, MTFRAE; >10-fold increase in minimal urticarial dose, MUDi; Visual Analogue Scale, VAS; 50% improvement from baseline measured on a visual analog scale, VAS50.*

°Inadequately controlled by H1-antihistamine at approved dose.

§Inadequately controlled with a doubled dose of H1-antihistamine.

^Inadequately controlled with H1-antihistamines at approved or increased doses alone or in combination with leukotriene receptor antagonists.

**Inadequately controlled with H1-antihistamines at approved or increased doses alone or in combination with H2-antihistamines or leukotriene receptor antagonists.*

Table 2.
Clinical Efficacy of Anti-IgE Antibodies in Phase II and III randomised controlled trials of Chronic Urticaria.

The results of the anti-IgE antibodies on CU in phase II and III randomised controlled trials [49, 50, 53, 54, 94, 112, 130–137] were summarized in **Table 2**.

Omalizumab 300 mg every 4 weeks, as add-on therapy, has demonstrated effective and safe in most, but not all, patients with CSU and there is evidence that this holds true for angioedema and CIndU. However, additional studies, using registries, real life settings and controlled trials should investigate personalized dosages and administration intervals, based on e. g. body mass index, UAS7 results, and on the identification of biomarkers able to predict changes in disease activity in response to therapy, for the development of tailored treatment algorithms to be used in clinical practice.

Current data of ligelizumab, being the next-generation anti-IgE antibody that is one-step ahead in clinical trials, are very promising and it has the potential to be a valid alternative for CSU patients unresponsive to omalizumab. If the phase III trial program confirms the superiority of ligelizumab compared to omalizumab, there is hope that symptoms might be controlled in all patients with CSU.

There are no licensed treatment options for CIndU and, therefore, recommended treatment is similar to CSU. However, off-label use of omalizumab has shown to be less effective compared to in CSU. Results from randomized controlled trials of ligelizumab for CIndU seem to be highly encouraging.

It will be intersting to see whether next-generation anti-IgE therapies are effective in CSU, CIndU and angioedema. The mechanism of action of the various anti-IgE approaches should be further elucidated in order to optimize the treatment of CU patients and its better understanding might enable targeted therapy in the near future.

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Nomenclature

AAS	Angioedema Activity Score.
AE-QoL	Angioedema Quality of Life.
AEs	Adverse Effects.

ASST	Autologous Serum Skin Test.
AU	Acute Urticaria.
BHRA	Basophil Histamine Release Assay.
CIndU	Chronic Inducible Urticaria.
CRACM1/ORAI1	Calcium Release-Activated Calcium Modulator 1.
CsA	Cyclosporine A.
CU	Chronic Urticaria.
CU-Q2oL	Chronic Urticaria Quality of Life.
CSU	Chronic Spontaneous Urticaria.
FcεRI	IgE Fc receptor.
H4R	Histamine H4 receptors.
HSS7	7 days Hives Severity Score.
Ig	Immunoglobulins.
IL	Interleukin.
ISS	Itch Severity Score.
ISS7	7 days Itch Severity Score.
OSMR	oncostatin M receptor.
QoL	Quality of Life.
TSLP	Thymic Stromal Lymphopoietin.
UAS	Urticaria Activity Score.
UAS7	7 days Urticaria Activity Score.
UCT	Urticaria Control Test.

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References

[1] Zuberier T, Aberer W, Asero R, et al. The EAACI/ GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018; 73(7):1393–1414. DOI: 10.1111/all.13397

[2] Deacock SJ. An approach to the patient with urticaria. Clin Exp Immunol. 2008;153(2):151–161. DOI: 10.1111/j.1365-2249.2008.03693.x

[3] Antia C, Baquerizo K, Korman A, Bernstein JA, Alikhan A. Urticaria: A comprehensive review: Epidemiology, diagnosis, and work-up. J Am Acad Dermatol. 2018;79(4):599–614. DOI: 10.1016/j.jaad.2018.01.020

[4] Zuberbier T, Maurer M. Urticaria: current opinions about etiology, diagnosis and therapy. Acta Derm Venereol. 2007;87(3):196–205. DOI: 10.2340/00015555-0240

[5] Mandel VD, Alicandro T, Pepe P, et al. Chronic Spontaneous Urticaria: A Review of Pathological Mechanisms, Diagnosis, Clinical Management, and Treatment EMJ. 2020;5(1):29–39.

[6] Balp MM, Weller K, Carboni V, Chirilov A, Papavassilis C, Severin T. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. Pediatr Allergy Immunol. 2018;29(6):630–636. DOI: 10.1111/pai.12910

[7] O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol. 1997;136(2):197–201.

[8] Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. Allergy. 2011;66(3):317–330. DOI: 10.1111/j.1398-9995.2010.02496.x

[9] Gonçalo M, Gimenéz-Arnau A, Al-Ahmad M, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol. 2021;184(2):226–236. DOI: 10.1111/bjd.19561

[10] Weller K, Giménez-Arnau A, Grattan C, et al. The Chronic Urticaria Registry: rationale, methods and initial implementation. J Eur Acad Dermatol Venereol. 2020 Sep 18. DOI: 10.1111/jdv.16947

[11] Weller K, Groffik A, Magerl M, et al. Development, validation and initial results of the Angioedema Activity Score. Allergy. 2013;68(9):1185–1192. DOI: 10.1111/all.12209

[12] Mandel VD, Guanti MB, Liberati S, Demonte A, Pellacani P, Pepe P. Omalizumab in chronic spontaneous urticaria refractory to conventional therapy: an italian retrospective clinical analysis with suggestions for long-term maintenance strategies. Dermatol Ther (Heidelb). 2018;8(2):291–301. DOI: 10.1007/s13555-018-0240-7

[13] Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review. J Allergy Clin Immunol Pract. 2018;6(2): 586–599. DOI: 10.1016/j.jaip.2017.07.017

[14] Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. Br J Dermatol. 2000;143(2):365–372. DOI: 10.1046/j.1365-2133.2000.03664.x

[15] Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P, Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial J Am Acad Dermatol. 2006;55(4):705–709. DOI: 10.1016/j.jaad.2006.04.078

[16] Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. Br J Dermatol. 2016;175(6):1153–1165. DOI: 10.1111/bjd.14768

[17] Curto-Barredo L, Archilla LR, Vives GR, Pujol RM, Giménez-Arnau AM. Clinical Features of Chronic Spontaneous Urticaria that Predict Disease Prognosis and Refractoriness to Standard Treatment. Acta Derm Venereol. 2018;98(7):641–647. DOI: 10.2340/00015555-2941

[18] Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S3–23. DOI: 10.1016/j.jaci.2009.12.980

[19] Schroeder HW Jr, Cavacini L. Structure and function of immunoglobulins. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S41–S52. DOI: 10.1016/j.jaci.2009.09.046

[20] Amarasekera M. Immunoglobulin E in health and disease. Asia Pac Allergy. 2011;1(1):12–15. DOI: 10.5415/apallergy.2011.1.1.12

[21] Hu J, Chen J, Ye L, Cai Z, Sun J, Ki K. Anti-IgE therapy for IgE-mediated allergic diseases: from neutralizing IgE antibodies to eliminating IgE(+) B cells. Clin Transl Allergy. 2018;8:27. DOI: 10.1186/s13601-018-0213-z

[22] Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. Nat Rev Immunol. 2014;14(4): 247–259. DOI: 10.1038/nri3632

[23] Ribatti D. The discovery of immunoglobulin E. Immunol Lett. 2016; 171:1–4. DOI: 10.1016/j.imlet.2016.01.001

[24] Dings RPM, Miller MC, Griffin RJ, Mayo KH. Galectins as Molecular Targets for Therapeutic Intervention. Int J Mol Sci. 2018;19(3):905. DOI: 10.3390/ijms19030905

[25] Kawakami T, Blank U. From IgE to Omalizumab. J Immunol. 2016;197(11): 4187–4192. DOI: 10.4049/jimmunol.1601476

[26] Johansson SG. The discovery of immunoglobulin e and its role in allergy. Chem Immunol Allergy. 2014;100:150–154. DOI: 10.1159/000358621

[27] Kaplan AP. Biologic agents in the treatment of urticaria. Curr Allergy Asthma Rep. 2012;12(4):288–291. DOI: 10.1007/s11882-012-0268-1

[28] Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. Theranostics. 2017;7(5):1266–1276. DOI: 10.7150/thno.18304

[29] Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. Clin Exp Allergy. 2009;39(6):777–787. DOI: 10.1111/j.1365-2222.2009.03256.x

[30] Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy. 2017;72(4):519–533. DOI: 10.1111/all.13083

[31] Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. J Allergy Clin Immunol. 2004;114(3): 527–530. DOI: 10.1016/j.jaci.2004.06.032

[32] Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. Int Arch

Allergy Immunol. 2017;172(1):40–44. DOI: 10.1159/000453453

[33] Serrano-Candelas E, Martinez-Aranguren R, Valero A, et al. Comparable actions of omalizumab on mast cells and basophils. Clin Exp Allergy. 2016;46(1):92–102. DOI: 10.1111/cea.12668

[34] Deza G, Bertolín-Colilla M, Pujol RM, et al. Basophil FcεRI Expression in Chronic Spontaneous Urticaria: A Potential Immunological Predictor of Response to Omalizumab Therapy. Acta Derm Venereol. 2017;97 (6):698–704. DOI: 10.2340/ 00015555-2654

[35] Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol.* 2017; 139(6):1772–1781.e1. DOI: 10.1016/j. jaci.2016.08.050

[36] Bar-Sela S, Reshef T, Mekori YA. IgE antithyroid microsomal antibodies in a patient with chronic urticaria. J Allergy Clin Immunol. 1999;103(6): 1216–1217. DOI: 10.1016/s0091-6749 (99)70204-6

[37] Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase–a novel pathomechanism of chronic spontaneous urticaria? PLoS One. 2011;6 (4):e14794. DOI: 10.1371/journal. pone.0014794

[38] Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. Allergy. 2017;72(10):1440–1460. DOI: 10.1111/all.13182

[39] Cugno M, Asero R, Ferrucci S, et al. Elevated IgE to tissue factor and thyroglobulin are abated by omalizumab in chronic spontaneous urticaria. Allergy. 2018;73(12):2408–2411. DOI: 10.1111/all.13587

[40] Schmetzer O, Lakin E, Topal FA, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol. 2018;142(3):876–882. DOI: 10.1016/j.jaci.2017.10.035

[41] Hatada Y, Kashiwakura J, Hayama K, et al. Significantly high levels of anti-dsDNA immunoglobulin E in sera and the ability of dsDNA to induce the degranulation of basophils from chronic urticaria patients. Int Arch Allergy Immunol. 2013;161(Suppl 2): 154–158. DOI: 10.1159/000350388

[42] Gruber BL, Baeza ML, Marchese MJ, Agnello V, Kaplan AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. J Invest Dermatol. 1988;90(2):213–217. DOI: 10.1111/1523-1747.ep12462239

[43] Grattan CE, Boon AP, Eady RA, Winkelmann RK. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. Int Arch Allergy Appl Immunol. 1990;93(2–3): 198–204. DOI: 10.1159/000235301

[44] Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. J Allergy Clin Immunol. 2001;107(6):1056–1062. DOI: 10.1067/mai.2001.115484

[45] Konstantinou GN, Asero R, Ferrer M, et al. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. Allergy. 2013;68(1):27–36. DOI: 10.1111/ all.12056

[46] Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective

clinical analysis. J Dermatol Sci. 2014;73 (1):57–62. DOI: 10.1016/j.jdermsci.2013. 08.011

[47] Asero R. Severe CSU and activation of the coagulation/fibrinolysis system: clinical aspects. *Eur Ann Allergy Clin Immunol.* 2019;52(1):15–17. DOI: 10.23822/EurAnnACI.1764-1489.109

[48] Yanase Y, Takahagi S, Hide M. Chronic spontaneous urticaria and the extrinsic coagulation system. Allergol Int. 2018;67(2):191–194. DOI: 10.1016/j. alit.2017.09.003

[49] Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol.* 2011;128(3):567–573.e1. DOI: 10.1016/j.jaci.2011.06.010

[50] Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202–209.e5. DOI: 10.1016/j.jaci.2011.04.038

[51] Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol. 2008;122(3):569–573. DOI: 10.1016/j. jaci.2008.07.006

[52] Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368:924–935. DOI: 10.1056/NEJMoa1215372

[53] Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/ spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol. 2013;132(1):101–109. DOI: 10.1016/j.jaci.2013.05.013

[54] Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67–75. DOI: 10.1038/ jid.2014.306

[55] Rottem M, Segal R, Kivity S, et al. Omalizumab therapy for chronic spontaneous urticaria: the Israeli experience. Isr Med Assoc J. 2014;16(8): 487–490.

[56] Sussman G, Hebert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. Ann Allergy Asthma Immunol. 2014;112(2):170–174. DOI: 10.1016/j.anai.2013.12.005

[57] Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. Expert Opin Biol Ther. 2013;13(9):1225–1228. DOI: 10.1517/ 14712598.2013.822484

[58] Giménez-Arnau AM, Toubi E, Marsland AM, Maurer M. Clinical management of urticaria using omalizumab: the first licensed biological therapy available for chronic spontaneous urticaria. J Eur Acad Dermatol Venereol. 2016;30(Suppl 5): 25–32. DOI: 10.1111/jdv.13697

[59] Gouveia PM, Gameiro A, Pinho A, Gonçalo M. Long-term management of chronic spontaneous urticaria with omalizumab. Clin Exp Dermatol. 2017; 42(7):735–742. DOI: 10.1111/ced.13173

[60] Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J Allergy Clin Immunol. 2016; 137(2):474–481. DOI: 10.1016/j.jaci. 2015.08.023

[61] Vadasz Z, Tal Y, Rotem M, et al. Omalizumab for severe chronic spontaneous urticaria: Real-life experiences of 280 patients. J Allergy Clin Immunol Pract. 2017;5(6):1743–1745. DOI: 10.1016/j.jaip.2017.08.035

[62] Marzano AV, Genovese G, Casazza G, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. J Eur Acad Dermatol Venereol. 2018;33(5):918–924. DOI: 10.1111/jdv.15350

[63] Giménez-Arnau AM, Santiago AV, Tomás JB, et al. Therapeutic Strategy According to Differences in Response to Omalizumab in Patients With Chronic Spontaneous Urticaria. *J Investig Allergol Clin Immunol.* 2019;29(5):338–348. DOI: 10.18176/jiaci.0323

[64] Eghrari-Sabet J, Sher E, Kavati A, et al. Real-world use of omalizumab in patients with chronic idiopathic/spontaneous urticaria in the United State. Allergy Asthma Proc. 2018;39(3):191–200. DOI: 10.2500/aap.2018.39.4132

[65] Hide M, Park HS, Igarashi A, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. J Dermatol Sci. 2017;87(1):70–78. DOI: 10.1016/j.jdermsci.2017.03.009

[66] Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol.* 2016;137(6):1742–1750.e4. DOI: 10.1016/j.jaci.2015.12.1342

[67] Ensina LF, Valle SO, Juliani AP, et al. Omalizumab in chronic spontaneous urticaria: a Brazilian real-life experience. Int Arch Allergy Immunol. 2016;169(2):121–124. DOI: 10.1159/000444985

[68] Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. Br J Dermatol. 2016;175(2):404–406. DOI: 10.1111/bjd.14540

[69] Giménez-Arnau A, Velasco M, Armario Hita JC, Labrador-Horrillo M, Silvestre Salvador JF. Omalizumab: what benefits should we expect? Eur J Dermatol. 2016;26(4):340–344. DOI: 10.1684/ejd.2016.2809.

[70] Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. JAMA Dermatol. 2014;150(3):288–290. DOI: 10.1001/jamadermatol.2013.8705

[71] Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. Theranostics. 2017;7(5):1266–1276. DOI: 10.7150/thno.18304

[72] Savic S, Marsland A, McKay D, et al. Retrospective case note review of chronic spontaneous urticaria outcomes and adverse effects in patients treated with omalizumab or ciclosporin in UK secondary care. Allergy Asthma Clin Immunol. 2015;11(1):21. DOI: 10.1186/s13223-015-0088-7.

[73] Song CH, Stern S, Giruparajah M, Berlin N, Sussman GL. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. Ann Allergy Asthma Immunol. 2013;110(2):113–117. DOI: 10.1016/j.anai.2012.11.022

[74] Türk M, Yilmaz I, Bahcecioglu SN. Treatment and retreatment with omalizumab in chronic spontaneous urticaria: real life experience with twenty-five patients. Allergol Int. 2017;67(1):85–89. DOI: 10.1016/j.alit.2017.05.003

[75] Grzanka R, Damasiewicz-Bodzek A, Kasperska-Zajac A. Interplay between acute phase response and coagulation/fibrinolysis in chronic spontaneous urticaria. Allergy Asthma Clin Immunol. 2018;14:27. DOI: 10.1186/s13223-018-0255-8

[76] Weller K, Ohanyan T, Hawro T, et al. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy. 2018;73(12):2406–2408. DOI: 10.1111/all.13586

[77] Gericke J, Metz M, Ohanyan T, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2017;139(3):1059–1061.e1. DOI: 10.1016/j.jaci.2016.07.047

[78] Palacios T, Stillman L, Borish L, Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. J Allergy Clinical Immunol Pract. 2016;4(3):529–530. DOI: 10.1016/j.jaip.2015.11.025

[79] Clayton E, Saltoun CA. Clinical Predictors of Response to Omalizumab for Treatment of Chronic Urticaria. J Allergy Clin Immunol. 2017;139(2):AB244. DOI: 10.1016/j.jaci.2016.12.785

[80] Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. Br J Dermatol. 2016;175(2):404–406. DOI: 10.1111/bjd.14540

[81] Asero R Canonica GW, Cristaudo A, et al. Critical appraisal of the unmet needs in the treatment of chronic spontaneous urticaria with omalizumab: an Italian perspective. Curr Opin Allergy Clin Immunol. 2017;17(6):453–459. DOI: 10.1097/ACI.0000000000000404

[82] Ferrer M, Boccon-Gibod I, Gonçalo M, et al. Expert opinion: defining response to omalizumab in patients with chronic spontaneous urticaria. Eur J Dermatol. 2017;27(5):455–463. DOI: 10.1684/ejd.2017.3085

[83] Tharp MD, Bernstein JA, Kavati A, et al. Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of "Real-world" Evidence. JAMA Dermatol. 2019;155(1):29–38. DOI: 10.1001/jamadermatol.2018.3447

[84] Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. Allergy. 2011;66(3):317–330. DOI: 10.1111/j.1398-9995.2010.02496.x

[85] Sussman G, Hébert J, Gulliver W, et al. Omalizumab Re-Treatment and Step-Up in Patients with Chronic Spontaneous Urticaria: OPTIMA Trial. *J Allergy Clin Immunol Pract.* 2020;8(7):2372–2378.e5. DOI: 10.1016/j.jaip.2020.03.022.

[86] Maurer M, Kaplan A, Rosén K, et al. The XTEND-CIU study: Long-term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol.* 2018;141(3):1138–1139.e7. DOI: 10.1016/j.jaci.2017.10.018

[87] Chen Y, Yu M, Huang X. Omalizumab treatment and outcomes in Chinese patients with chronic spontaneous urticaria, chronic inducible urticaria, or both. World Allergy Organ J. 2021;14(1):100501. DOI: 10.1016/j.waojou.2020.100501

[88] Arm JP, Bottoli I, Skerjanec A, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy. 2014;44(11):1371–1385. DOI: 10.1111/cea.12400

[89] Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001;108(2): 184–190. DOI: 10.1067/mai.2001.117880

[90] Gauvreau GM, Arm JP, Boulet L-P, et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. J Allergy Clin Immunol. 2016;138(4):1051–1059. DOI: 10.1016/j.jaci.2016.02.027

[91] Gasser P, Tarchevskaya SS, Guntern P, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat Commun. 2020; 11(1):165. DOI: 10.1038/s41467-019-13815-w

[92] Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nat Rev Immunol. 2008;8(3), 205–217. DOI: 10.1038/nri2273

[93] Coyle AJ, Wagner K, Bertrand C, Tsuyuki S, Bews J, Heusser C. Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. J Exp Med. 1996;183 (4):1303–1310. DOI: 10.1084/jem.183.4.1303

[94] Maurer M, Giménez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. N Engl J Med. 2019;381 (14):1321–1332. DOI: 10.1056/NEJMoa190040898

[95] Bernstein JA, Baker D, Maurer M, et al. Ligelizumab achieves sustained control of chronic spontaneous urticaria symptoms of hives, itch and angioedema: 1-year treatment results. Allergy. 2019;74(S106):21. DOI: 10.1111/all.1395799.

[96] Soong W, Metz M, Bernstein JA, et al. Long-term treatment with ligelizumab achieves prolonged symptom control in patients with chronic spontaneous urticaria during the post-treatment follow-up. J Allergy Clin Immunol. 2020;145(2):AB341. DOI: 10.1016/j.jaci.2019.12.077100

[97] Giménez-Arnau AM, Salman A. Targeted Therapy for Chronıc Spontaneous Urtıcarıa: Ratıonale and Recent Progress. Drugs. 2020;80(16): 1617–1634. DOI: 10.1007/s40265-020-01387-9

[98] Severin T, Maurer M, Giménez-Arnau AM, et al. Study design and rationale of a phase 3b extension study of ligelizumab in adult and adolescent patients with chronic spontaneous urticaria. Allergy. 2020;75(S109):446. DOI: 10.1111/all.14508

[99] Ensina LF, Cusato-Ensina AP, Camelo-Nunes IC, Solé D. Omalizumab as third-line therapy for urticaria during pregnancy. *J Investig Allergol Clin Immunol*. 2017;27(5):326–327. DOI: 10.18176/jiaci.0179

[100] Ghazanfar MN, Thomsen SF. Successful and safe treatment of chronic spontaneous urticaria with omalizumab in a woman during two consecutive pregnancies. Case Rep Med. 2015;2015: 368053. DOI:10.1155/2015/36805350.

[101] Gonzalez-Medina M, Curto-Barredo L, Labrador-Horrillo M, Giménez-Arnau A. Omalizumab use during pregnancy for chronic spontaneous urticaria (CSU): report of two cases. J Eur Acad Dermatol Venereol. 2017;31(5):e245-e246. DOI: 10.1111/jdv.14034

[102] Namazy JA, Blais L, Andrews EB, et al. Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. *J Allergy Clin Immunol.* 2020;145(2):528–536.e1. DOI: 10.1016/j.jaci.2019.05.019

[103] Passanisi S, Arasi S, Caminiti L, Crisafulli G, Salzano G, Pajno GB. Omalizumab in children and adolescents with chronic spontaneous urticaria: case series and review of the literature. Dermatol Ther. 2020;33(4): e13489. DOI: 10.1111/dth.13489

[104] Ari A, Levy Y, Segal N, et al. Efficacy of omalizumab treatment for pediatric chronic spontaneous urticaria: a multi-center retrospective case series. Pediatr Dermatol. 2020;37(6):1051–1054. DOI: 10.1111/pde.1436042

[105] Nettis E, Cegolon L, Di Leo E, Canonica WG, Detoraki A, Italian OCUReL Study Group. Omalizumab in elderly patients with chronic spontaneous urticaria: An Italian real-life experience. Ann Allergy Asthma Immunol. 2018;120(3):318–323. DOI: 10.1016/j.anai.2017.12.007

[106] Vollono L, Piccolo A, Lanna C, et al. Omalizumab for chronic spontaneous urticaria in "complex" patients: data from real-life clinical practice. Drug Des Devel Ther. 2019;13: 3181–3186. DOI:10.2147/DDDT.S21430766

[107] Larenas-Linnemann D, Saini SS, Azamar-Jácome AA, Maurer M. Chronic urticaria can be caused by cancer and resolves with its cure. Allergy. 2018;73 (7):1562–1566. DOI:10.1111/all.13434

[108] Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgereit T, Maurer M. How to treat patients with chronic spontaneous urticaria with omalizumab: questions and answers. J Allergy Clin Immunol Pract. 2020;8(1): 113–124. DOI: 10.1016/j.jaip.2019.07.021

[109] Kocatürk E, Zuberbier T. New biologics in the treatment of urticaria. Curr Opin Allergy Clin Immunol. 2018; 18(5):425–431. DOI: 10.1097/ACI.0000000000000466

[110] Scheerens H, Putnam W, Zheng Y, et al. Treatment with MEMP1972A, an anti-M1 prime monoclonal antibody, reduced serum IgE in healthy volunteers and patients with allergic rhinitis. Am J Respir Crit Care Med. 2012;185: A6791.109.

[111] Gauvreau GM, Harris JM, Boulet LP, et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Sci Transl Med.* 2014;6(243):243ra85. DOI: 10.1126/scitranslmed.3008961

[112] Harris JM, Cabanski CR, Scheerens H, et al. A randomized trial of quilizumab in adults with refractory chronic spontaneous urticaria. J Allergy Clin Immunol. 2016;138(6):1730–1732. DOI: 10.1016/j.jaci.2016.06.023111

[113] Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol. 1999;104(1):169-172. DOI: 10.1016/s0091-6749(99)70129-6

[114] Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. J Allergy Clin Immunol. 2002;109(1):114–118. DOI: 10.1067/mai.2002.120954

[115] Korosec P, Subic T, Adamic K, Silar M, Kosnik M. C5a-induced in vitro basophil activation in patients with chronic urticaria: a pilot study. Wien Klin Wochenschr. 2009;121(9–10):339–343. DOI: 10.1007/s00508-009-1168-9

[116] Huber M, Helgason CD, Damen JE, Liu L, Humphries RK, Krystal G. The src homology 2-containing inositol phosphatase (SHIP) is the gatekeeper of mast cell degranulation. Proc Natl Acad Sci USA. 1998;95(19):11330–11335. DOI: 10.1073/pnas.95.19.1133

[117] Cherwinski HM, Murphy CA, Joyce BL, et al. The CD200 receptor is a novel and potent regulator of murine and human mast cell function. J

Immunol. 2005;174:1348–1356. DOI: 10.4049/jimmunol.174.3.1348

[118] Zampeli E, Tiligada E. The role of histamine H4 receptor in immune and inflammatory disorders. Br J Pharmacol. 2009;157:24–33. DOI: 10.1111/j.1476-5381.2009.00151.x

[119] Cowden JM, Zhang M, Dunford PJ, Thurmond RL. The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. J Invest Dermatol. 2010; 130(4):1023–1033. DOI: 10.1038/jid.2009.358

[120] Werfel T, Layton G, Yeadon M, et al. Efficacy and safety of the histamine H4 receptor antagonist ZPL-3893787 in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2019; 143(5):1830–1837.e4. DOI: 10.1016/j.jaci.2018.07.047

[121] Gangemi S, Quartuccio S, Casciaro M, Trapani G, Minciullo PL, Imbalzano E. Interleukin 31 and skin diseases: a systematic review. Allergy Asthma Proc. 2017;38:401–408. DOI: 10.2500/aap.2017.38.4080

[122] Luo XY, Liu Q, Yang H, et al. OSMR gene effect on the pathogenesis of chronic autoimmune Urticaria via the JAK/STAT3 pathway. Mol Med. 2018;24 (1):28. DOI: 10.1186/s10020-018-0025-6

[123] Kasperska-Zajac A, Sztylc J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. Clin Exp Allergy. 2011;41(10):1386–1391. DOI: 10.1111/j.1365-2222.2011.03789.x.

[124] Krause K, Feist E, Fiene M, Kallinich T, Maurer M. Complete remission in 3 of 3 anti-IL-6-treated patients with Schnitzler syndrome. J Allergy Clin Immunol. 2012;129(3):848–850. DOI: 10.1016/j.jaci.2011.10.031

[125] Fujisawa D, Kashiwakura J-I, Kita H, et al. Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. *J Allergy Clin Immunol.* 2014; 134(3):622–633.e9. DOI: 10.1016/j.jaci.2014.05.004

[126] Ständer S, Siepmann D, Herrgott I, Sunderkötter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. PLoS One. 2010;5(6):e10968. DOI: 10.1371/journal.pone.0010968

[127] Takai T. TSLP expression: cellular sources, triggers, and regulatory mechanisms. Allergol Int. 2012;61:3–17. DOI: 10.2332/allergolint.11-RAI-0395

[128] Yan S, Chen W, Zhang Y, Li J, Chen X. Calcium release-activated calcium modulator 1 as a therapeutic target in allergic skin diseases. Life Sci. 2019;228:152–157. DOI: 10.1016/j.lfs.2019.05.001

[129] Li J, Guo A, Chen W, et al. Association of ORAI1 gene polymorphisms with chronic spontaneous urticaria and the efficacy of the nonsedating H1 antihistamine desloratadine. *J Allergy Clin Immunol.* 2017;139(4):1386–1388.e9. DOI: 10.1016/j.jaci.2016.10.017

[130] Metz M, Torene R, Kaiser S, et al. Omalizumab normalizes the gene expression signature of lesional skin in patients with chronic spontaneous urticaria: a randomized, double-blind, placebo-controlled study. Allergy. 2019; 74(1):141–151. DOI: 10.1111/all.13547118

[131] Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1 -antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. Allergy.

2016;71(8):1135–1144. DOI: 10.1111/all.12870119

[132] Staubach P, Metz M, Chapman-Rothe N, et al. Omalizumab rapidly improves angioedema-related quality of life in adult patients with chronic spontaneous urticaria: X-ACT study data. Allergy. 2018;73(3):576–584. DOI: 10.1111/all.13339

[133] Hide M, Igarashi A, Yagami A, et al. Efficacy and safety of omalizumab for the treatment of refractory chronic spontaneous urticaria in japanese patients: subgroup analysis of the phase 3 POLARIS study. Allergol Int. 2018;67(2):243–252. DOI: 10.1016/j.alit.2017.10.001

[134] Maurer M, Schutz A, Weller K, et al. Omalizumab is effective in symptomatic dermographism-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol.* 2017;140(3):870–873.e5. DOI: 10.1016/j.jaci.2017.01.042

[135] Gastaminza G, Azofra J, Nunez-Cordoba JM, et al. Efficacy and safety of omalizumab (xolair) for cholinergic urticaria in patients unresponsive to a double dose of antihistamines: a randomized mixed double-blind and open-label placebo-controlled clinical trial. *J Allergy Clin Immunol Pract.* 2019;7(5):1599–1609.e1. DOI: 10.1016/j.jaip.2018.12.025

[136] Metz M, Schutz A, Weller K, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol.* 2017;140(3):864–867.e5. DOI: 10.1016/j.jaci.2017.01.043

[137] Aubin F, Avenel-Audran M, Jeanmougin M, et al. Omalizumab in patients with severe and refractory solar urticaria: a Phase II multicentric study. J Am Acad Dermatol. 2016;74(3):574–575. DOI: 10.1016/j.jaad.2015.11.021124