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New Biological Treatment Options in CSU

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Abstract

Chronic spontaneous urticaria (CSU) is a devastating disease and is associated with many co-morbidities and long-lasting suffering. Therefore, patients always look for a most efficient therapeutic approach to achieve a full remission. In many patients, CSU remain refractory to off-label doses of antihistamines and short courses of steroids, and therefore are treated with omalizumab. However, 15–20% of severe CSU patients will stay unresponsive to omalizumab and are defined as being of un-met needs. In this review we will shed light on the many new drugs which are assessed in ongoing clinical trials.

Keywords: Chronic spontaneous urticaria, T-cells, autoimmunity, treatment

1. Introduction

Chronic spontaneous urticarial (CSU) with or without angioedema, is a condition which lasts more than 6 weeks, without an apparent trigger. It results from a pathogenic over-activation of dermal mast cells and basophils, followed by their degranulation and the release of pro-inflammatory mediators (mainly histamine) inducing the appearance of transient itchy wheals, and occasionally episodes of angioedema. The prevalence of CSU is estimated to be between 0.5-1percent in the general population, with an incidence of 0.10 to 1.50 per 1000 person-years. It predominantly affects female, with symptom onset occurring mainly between 20 and 40 years [1]. Earlier studies reported on CSU lasting over one year in more than 70% of cases and continuing to exist in 14% of them after five years. CSU duration was associated with the presence of angioedema and disease severity. In a recent study, younger CSU patients (22 ± 16 years) tended to have a significantly longer course, were in 16% of patients, CSU symptoms lasted over ten years [2, 3]. In addition to its prolonged duration, CSU severely affects quality of life and is associated with comorbidities such as lack of sleep, impairments in work productivity, and depression/anxiety. In one study about 50% of patients with CSU were diagnosed with one or more psychosomatic disorders, the most frequent of which was anxiety, followed by depressive and somatoform disorders [4, 5]. The prevalence of rheumatoid arthritis, systemic lupus erythematosus, thyroiditis and vitiligo were found to be significantly increased in CSU patients [6]. Patients without any evidence of comorbidities at the time of their CSU diagnosis had an increased risk of developing mast cell-mediated diseases including atopic diseases [7]. Many studies have focused on the importance of clinical and laboratory biomarkers for the assessment of CSU severity and the evaluation of treatment efficacy. Clinical manifestations such as asthma and thyroid disease were associated

with higher disease severity and duration [8]. Laboratory markers, namely, C-reactive protein (CRP), autologous serum skin test (ASST), basophil activation test (BAT, D-dimer levels and total serum IgE are all potential blood biomarkers that are useful for CSU management [9]. Many CSU patients continue to suffer from symptoms of pruritus, urticaria, and angioedema despite the acceptable up dosing of second-generation antihistamines (up to fourfold) [10]. Recurrent short courses of steroids were also reported to have only a short-term beneficial effect in severe CSU patients. Current treatments are considerably effective in achieving good response and favorable remission, however, many CSU patients are still refractory to these available treatments. This is why, it is extremely important to identify and understand underlying disease mechanisms, in order to achieve better therapeutic outcomes. In addition to a brief summary covering the pathogenesis of CSU, and the currently used therapies, this chapter will focus on emerging new therapies, some of which are being studied in on-going clinical trials, and others that are being assessed as potential candidates for treatment.

2. Pathophysiology

At the very beginning (four decades ago), CSU was considered to be a T-cell mediated disorder, supported by the finding of rich CD4+ T-cell infiltration in the skin of CSU patients [11]. The involvement of activated T-cells in peripheral blood of CSU patients, namely the increased expression of CD40 ligand on T-cells similarly to what we find on activated T-cells from patients suffering from active systemic lupus erythematosus and other autoimmune diseases was also reported [12]. In concert with this, there are studies showing an increased switch of Th1 to Th17 in the peripheral blood of CSU patients in correlation with CSU disease severity, and IL-17 levels are significantly higher in the autologous serum skin test (ASST) positive than ASST negative CSU patients. Plasma levels of interferon- γ (IFN- γ), IL-2 and IL-21 were also found to be significantly higher in ASST-positive CSU subgroups, known to involve the positive regulation of the Janus-kinase-signal transducer and activator of transcription (JAK/STAT) signaling pathway [13]. In a recent study using Kunming mice (a model of CSU), a longer duration and higher intensity of pruritus was demonstrated to be in association with enhanced levels of eosinophils, inflammatory cytokine expression and activated the JAK/STAT signaling pathway. This was found to be in mice overexpressing IL-9 and IL-10, contributing to the development of CSU by signaling the JAK/STAT pathway [14]. Commensurate with this, is the later finding of antigen/disease-specific auto-reactive CD4 + T cells that target Fc ϵ RI α in most patients with CSU, with a cytokine secretion profile typical of a Th1 immune response. This is compatible with the earlier finding of IgG autoantibodies to Fc ϵ RI α on dermal mast cells and basophils, supporting the concept that CSU is an autoimmune disorder probably mediated by auto-reactive T cells. IFN- γ and autoantibody responses to Fc ϵ RI α were found to be inversely related, with IFN- γ responses being detected earlier than autoantibodies in the course of CSU. This finding of inverse relationship between auto-reactive T-cell responses and autoimmunity suggests these responses to be different stages in the pathogenesis of CSU [15]. In a very recent study we found that increased numbers of CD4 + T cells and mast cells were present in both lesional and non-lesional skin of CSU patients when compared with the healthy controls. Both types of cells were strongly positive for IL-17A and found to be in close proximity to each other [16]. With respect to the aforementioned, autoimmunity in CSU patients is reported to be found in at least 50% of cases. Two types of autoimmunity have been documented and supported by numerous reports. The first (type I) is driven by

IgE auto-antibodies against thyroid antigens and/or auto-allergens, defined by the presence of anti-TPO antibodies. In parallel to this, is the finding of type IIb auto-immunity characterized by the binding of IgG auto-antibodies (recently also IgA and Ig M) to IgE and/or FcεRIα on mast cells [17–19]. Both types are followed by the intense activation and degranulation of mast cells and the release of inflammatory mediators in the skin that are able to induce itchy wheals and angioedema. Among the many mediated agents, histamine, pro-inflammatory cytokines and chemokines are the most frequent [20]. Basophils and Eosinophils have recently been included among other cells actively involved in the pathogenesis of CSU. In this respect, peripheral blood basopenia is frequently reported in association with CSU disease severity. It has been postulated that this is a result of the migration of basophils from blood to the skin of active CSU patients. Basopenia resolves in parallel with CSU remission and therefore may become a suitable marker for follow-up [21]. Recent evidence suggests that eosinophils may also play role in the pathogenesis of CSU. Both eosinophils and eosinophil granules were displayed in lesional skin of CSU patients. This is in contrast to allergic rhinitis and asthma where peripheral blood eosinophilia is a characteristic finding, while in CSU, peripheral blood eosinopenia is observed in association with disease severity. As in the case of basopenia, depletion of active eosinophils and their shift to the skin of CSU patients is the most accepted mechanism of this phenomenon [22]. The issue of how all these cells, and mechanisms, are linked, and how they act at onset or during the persistence of CSU is extremely complex. However, current therapies, targeting free IgE, mast cells and T cells are reported to be tremendously efficient in inducing CSU remission.

3. Current therapies for CSU

The introduction of the non-sedative anti-histamines replacing the first generation (sedative) one was a giant step forward in the treatment of CSU. At a later date, H1-antihistamine up-dosing was established and shown to be safe and of better efficacy. However, even when up-dosing was increased fourfold, the rate of non-responders remained high, thereby suggesting that additional treatments were needed [23]. As early as 1991, targeting T-cells by cyclosporine A (CsA) was shown to be highly effective in severe cases of CSU [24]. Later on, we demonstrated that low doses of CsA (2–3 mg/ml) given for three months were both extremely beneficial and had a low prevalence of side-effects. In some patients, we could demonstrate a long-lasting full remission, while in others it was even curative [25]. The efficacy of CsA was established by many double-blind, randomized studies. Symptom scores significantly improved in the CsA group over with placebo. CsA was well tolerated at daily doses of 3 mg/kg. Side effects such as hypertension and increased serum creatinine were rare [26]. In addition, the efficacy and safety of CsA in CSU was evaluated by a meta-analysis of eighteen studies. A low-dose (2–3 mg/kg/d) was considered to be both beneficial and safe, and adverse events appear to be dose dependent and occur more frequently in patients that have been treated with moderate doses (4–5 mg/kg/d) [27]. In a recent study, the prediction of beneficial response to CsA treatment, was assessed using, positive ASST, plasma D-dimer levels, IL-2, IL-5 levels and total IgE level. Decreased plasma D-dimer levels, and decreased serum IL-2 and IL-5 were reported to be correlated with clinical improvement after CsA treatment [28]. While cyclosporine A is still used in cases with severe CSU, the fear of side effects, mainly in those with mild hypertension or diabetes, has limited its usage, allowing omalizumab (an IgG-anti-IgE monoclonal antibody), approved for the treatment of anti-histamine-refractory CSU in 2014 to become the preferable option in treating CSU. In the European

Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and World Allergy (EAACI/GA2LEN/EDF/WAO) guidelines for the treatment of CSU, it is recommended that omalizumab should be added to off-label doses of anti-histamines when CSU is inadequately controlled [29, 30]. Cyclosporine A remains the final option for those considered to be omalizumab failures. The main mechanism through which omalizumab acts, is its ability to bind soluble IgE and the down regulation of FcεRI expression on skin mast cells. This is followed by decreased mast cell activation and degranulation. In this respect, higher levels of FcεRI expression, predict a faster response to omalizumab. In addition higher levels of total serum IgE were shown to be associated with a greater responsiveness to omalizumab [31]. While it is well accepted that a complete response to the standard dose of omalizumab (300 mg/month) is observed in about 59% of patients, 15% of treated patients still remain resistant to this dose of omalizumab [32]. In many studies, up dosing of omalizumab to 450 mg/month was shown to achieve better clinical responses with a good safety profile [33]. Options of higher doses of cyclosporine A or the combination of omalizumab and cyclosporine A were also reported in few case reports in severe and refractory to all of the above mentioned approaches. Un-met needs and the requirement for new treatments in still refractory CSU are the subject of many on-going clinical trials in which targeting new relevant pathways is assessed.

4. New drugs in ongoing clinical trials

4.1 Anti IgE

4.1.1 Ligelizumab

Ligelizumab (QGE031) is a new monoclonal antibody directed against the Cε3 domain of IgE, which in preclinical and in phase I clinical studies demonstrated its 50-fold greater affinity to IgE in vitro and six- to nine-fold greater potency in vivo compared to omalizumab. This affinity difference is caused due to epitope differences between ligelizumab and omalizumab that contribute to their distinct qualitative IgE-receptor profiles. Ligelizumab was superior in its ability to suppress IgE binding to FcεRI, basophil activation, and IgE secretion by B cells [34]. It was also shown that Ligelizumab provided a longer suppression of free and cell-bound IgE [35]. Omalizumab was shown to inhibit the interaction of IgE-FcεRII (CD23) more efficiently than Omalizumab, and this finding might explain the superior anti-asthmatic effect of omalizumab, considering the role of CD23 in lung inflammation [34]. In order to further assess its efficacy in CSU, a phase IIb dose-finding trial was designed for the efficacy and safety of ligelizumab. Doses of 24 mg, 72 mg, and 240 mg every four weeks were compared to the omalizumab standard dose of 300 mg every four weeks and to placebo in 382 adult patients with CSU. Clinical beneficial effects were evaluated by using - UAS7 (Urticaria Activity Score) and HSS7 (Hives Severity Score). The percentage of patients with a complete control of their hives (HSS7:0) and a complete control of their symptoms (UAS7:0) at week 12 was significantly higher in all ligelizumab arms (24 mg, 72 mg, 240 mg) compared with omalizumab (300 mg) and the placebo. The question regarding the low complete response rates with omalizumab was attributed to the high percentage of patients with an autoimmune pattern and angioedema. Adverse events rates were similar in all groups, except for a slightly higher incidence of local reaction at the injection site of ligelizumab 240 mg compared to omalizumab [36]. Patient's follow up in this clinical study revealed that among patients who achieved an UAS7 ≤ 6 at

week 20, the beneficial therapeutic response was maintained for a median of 16, 8 and 8 weeks with ligelizumab 240 mg, 72 mg, and omalizumab, respectively. In addition, a 1-year extension phase of the above clinical study showed that in patients with $UAS7 \geq 12$ who received ligelizumab 240 mg every 4 weeks (NCT02649218), the $UAS7 \leq 6$ score response was maintained for a median period of 28 weeks [37]. Moreover, the treatment with ligelizumab was superior in other clinical measures when compared with omalizumab, namely, a decrease in the use of rescue medication [38] a greater and sustained efficacy in reducing angioedema at week 12 (the percentage of angioedema-free patients with ligelizumab 72 mg, 240 mg, omalizumab 300 mg, and placebo, was 87.5%, 94.9%, 76.3%, and 68.3%, respectively [39]. Several Phase III clinical trials (NCT03580356, NCT03580369, NCT03437278, NCT04210843) are currently in progress in order to further investigate the efficacy and safety of ligelizumab 72 mg and 120 mg when compared with omalizumab 300 mg and a placebo in CSU adolescent and adult patients up to 52 weeks. In Japan, in adult CSU patients who failed to response to H1-anti-histamines, are part of another phase III, open-label, and single-arm study of ligelizumab that is currently in progress (NCT03907878). It is hopeful that these studies and the extension phase study with ligelizumab will better characterize its usage in re-treatment, and self-administration, as well as its benefit as a monotherapy.

4.1.2 UB-221

Another new monoclonal antibody against IgE, UB-221, has up to eightfold greater affinity for free IgE in comparison with omalizumab. This new compound is currently being investigated for safety, tolerability, pharmacodynamics and pharmacokinetics in an ongoing phase I clinical trial in adult patients with CSU. The study is composed of single doses [0.2, 0.6, 2, 6, 10 mg/kg UB-221] given intravenously (IV) vs. a placebo (NCT03632291, NCT04175704) [40].

4.2 B cells

4.2.1 Bruton's tyrosine kinase (BTK) inhibitors

Bruton tyrosine kinase (BTK) is a tyrosine kinase which was found to play a major role in B cell development. At a later date, it was found to be expressed in various hematopoietic cells including macrophages, mast cells, and basophils. In the context of CSU pathogenesis, BTK was also found to play a major role in the FcεR activation and signaling in mast cells [41, 42]. BTK inhibitors are widely used today to treat several B cell malignancies and auto immune disorders [43]. Out of the many known BTK inhibitors, four (ibrutinib, dasatinib, AVL-292, CNX-774) are recognized to be effective suppressors of IgE-induced activation and histamine release from basophils and mast cells [44]. Ibrutinib (420 mg/day), was assessed in patients suffering from peanut/tree nut allergy and reported to suppress skin test responses to these food allergens within seven days, and without any discernable adverse events. No serious adverse events 100. Upon considering of the pivotal role of FcεRI signaling in CSU, it seems that the use of BTK inhibitors for CSU could be a potential new treatment option. LOU064 (remibrutinib), a more selective BTK inhibitor is being investigated in ongoing phase II clinical trials (NCT03926611, NCT04109313) for its efficacy and safety in adult patients with CSU. In an in-vitro study, the binding of BTK by remibrutinib was more efficient than fenebrutinib, thus it has a faster onset of action and its effects are maintained longer [45]. Another phase II study, investigating a new BTK inhibitor (fenebrutinib 200 mg orally twice a day), in adult patients suffering from CSU, has recently been

completed. The results of this study indicated that at week 8, a marked improvement of the UAS7 was achieved at 200 mg twice a day compared with the placebo group [33].

4.2.2 Anti-CD20

Rituximab (RTX) is a well-known monoclonal antibody directed against CD20. It causes the depletion of mature and memory B cells through several mechanisms such as CDC and ADCC. For many years, it has been used to treat B cell hematological malignancies and autoimmune diseases such as- rheumatoid arthritis (RA), and pemphigus vulgaris [46]. Due to the autoimmune nature of CSU, it seems reasonable that the reduction of memory B cells and a subsequent decrease of the autoantibodies due to Rituximab, could well become a beneficial treatment option, particularly in autoimmune CSU. So far, only five patients in whom severe CSU refractory to immunosuppressive treatments, have been treated with rituximab [47–51]. The treatment regimen in these patients was either as used in lymphoma (375 mg/m² weekly for 4 weeks) or as used in the RA protocol (two doses of 1000 mg with a 2-week interval). Four patients responded well to this treatment, and only one failed. However, a phase I/II open-label trial (NCT00216762) was terminated due to safety concerns. To date, there are no ongoing clinical trials on Rituximab in CSU patients. It appears that Rituximab could be reserved for future use as an alternative treatment option in patients with very severe, and treatment-resistant CSU.

4.3 Basophils, eosinophils and Th2 cells

4.3.1 Chemo attractant receptor-homologous molecule expressed on Th2 (CRTH2) inhibitors

CRTH2 is the prostaglandin D₂ (PGD₂) receptor that is secreted from mast cells upon activation and degranulation. CRTH2 is normally expressed on eosinophils, basophils, and Th2 cells. The signaling pathways following PGD₂-interaction\ligation to CRTH2 results in the stimulation and chemotaxis of basophils and eosinophils, Th2 response, and the increase in the amount of histamine released from basophils [52, 53]. In patients suffering from CSU, membrane CRTH2 expression on basophils and eosinophils, was found to be extremely low, which was presumably attributed to the internalization of CRTH2 upon PGD₂ binding. These results suggested a role for PGD₂ via CRTH2 ligation in CSU [54]. A particular CRTH2 gene polymorphism was demonstrated in several patients suffering from CSU, and these specific patients needed high doses of anti-histamines in order to control CSU [53]. These findings further establish a role for CRTH2 in CSU pathogenesis, suggesting the relevance of its targeting. Based on these considerations, a new oral CRTH2 antagonist, AZD1981, was generated and used for the treatment of CSU in a clinical trial. In a phase II, double-blind, placebo-controlled trial, twenty-six CSU patients were enrolled and completed the 4-week treatment period with either AZD1981 (40 mg three times daily) or a placebo. A clinical assessment of UAS7 and ISS7 scores revealed a significant reduction in these scores when compared with the baseline scores before treatment. However, the primary endpoint (a reduction in UAS7 $\geq$ 9.5 points when compared with the baseline) was not achieved in this study. No significant differences were observed in terms of anti-histamines use or the frequency of angioedema-attacks between the treatment and control groups. No serious adverse events were observed and the overall treatment was well tolerated [52]. Regarding biological effects, the treatment with AZD1981 significantly

inhibited PGD2-mediated eosinophil migration to the skin. Despite failing to meet the primary endpoint, future studies evaluating the efficacy of AZD1981 with longer treatment duration and higher doses are needed.

4.3.2 Spleen tyrosine kinase (SYK) inhibitors

Spleen tyrosine kinase (SYK) is a pivotal player that regulates histamine release and the synthesis of immune mediators (e.g. leukotriene, prostaglandin) upon FcεRI activation in mast cells [55]. Nowadays, oral SYK inhibitors such as fostamatinib are used extensively in the treatment for autoimmune diseases such as immune thrombocytopenic purpura, chronic graft-versus-host disease and Rheumatoid Arthritis. A new intranasal SYK inhibitor, R112, was also proven to suppress FcεRI-related mediator release following mast cell degranulation, thereby suggesting that SYK inhibitors are extremely efficient in suppressing mast cell degranulation [56]. Based on the above data the use of SYK inhibitors to successfully treat CSU patients was not surprising. The first study to use SYK inhibitors was an in vitro study where a topical SYK inhibitor, was used in an ex vivo human skin model, GSK2646264. In this study it was shown that this inhibitor blocked the histamine release from mast cells through IgE signaling [57]. Following this study, a randomized, placebo-controlled phase I trial (NCT02424799) was conducted in order to evaluate the efficacy and safety of GSK2646264 0.5% and 1% topical cream in patients with CSU and cold urticarial. The results of this study are not available yet. In another in vitro study, the expression level of SYK was evaluated in mast cells from CSU patients. These patients were categorized according to the clinical outcome as responders and non-responders; the degree of basophil's histamine release and the expression of SYK protein in mast cells. This study found that the SYK protein was expressed significantly higher in responders when compared with non-responders and healthy controls. It also revealed that the increased expression of SYK was correlated with the spontaneous histamine release from mast cells in these patients [58].

4.4 Cytokine inhibitors

4.4.1 Anti IL-1

The IL-1 cytokine family in general and IL-1α and IL-1β, specifically have pro-inflammatory effects, which are neutralized by using the IL-1R antagonist. [59]. Several IL-1 mutations (NLRP3 genes) are collectively defined as auto-inflammatory syndromes, which cause the increased secretion of IL-1β. This is associated with a heterogeneous syndrome (NLRP3-AID (consisting of familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological, cutaneous and articular syndrome. The urticarial-like rash is one of most common hallmarks of these syndromes [60, 61]. IL-1 inhibitors, such as canakinumab (monoclonal antibody against of IL-1β), anakinra (recombinant IL-1R antagonist), and rilonacept (IL-1α/β blocker) are very effective in reducing inflammation and the clinical spectrum of these syndromes [62]. It is worth mentioning, that the emerging knowledge regarding the use of IL-1-blocking agents in the treatment of Schnitzler's syndrome, is characterized by the presence of urticarial rash and systemic inflammation [63, 64]. In on-going clinical trials, the effectiveness and safety of RPH-104 (a novel molecule against IL-1β), rilonacept, and canakinumab has been confirmed in Schnitzler syndrome (NCT04213274), acquired cold-contact urticaria (NCT02171416), and CSU (NCT01635127). The results of these trials have not yet been published. In few sporadic reports, anti-IL-1drugs were shown to

be beneficial in CSU patients, who remained resistant to all classical therapies for CSU [65]. A new somatic mutation in NLRP3 was recently reported in two elderly patients with long-standing, refractory CSU associated with fever and increased CRP. Both of these patients improved dramatically following the usage of anakinra. As a result, it is assumed that in patients with refractory urticaria and markers of systemic inflammation (a possible underlying NLRP3-related disorder), anti-IL-1 treatment requires further evaluation [66].

4.4.2 Anti-IL-4/13

In the process of Th2 differentiation several cytokines are produced. The most important cytokines in this process are interleukin-4 and IL-13 [59]. Dupilumab, a new monoclonal antibody directed against the alpha subunit of IL-4 and IL-13 receptors, was recently approved for the treatment of asthma, nasal polyposis, and atopic dermatitis [67]. Increased levels of IL-4 were recently demonstrated in patients with CSU, thereby suggesting a pathogenic role of both Th1/Th2 responses and raising the option of treating CSU with Dupilumab [68]. A recent case report involving six patients with concomitant atopic dermatitis and CSU who were refractory to high dose of omalizumab (600 mg\4 weeks) documented their successful treated with Dupilumab. In this report, it was postulated that the beneficial therapeutic effect of Dupilumab could be the result of its blocking Th2 inflammatory pathways by inhibiting IL-4 and IL-13, respective [69]. Currently, there are three ongoing, phase II/III clinical studies investigating the efficacy and safety of Dupilumab in CSU (NCT03749135, NCT04180488 (EFC16461-CUPID)) and cholinergic urticaria (NCT03749148) unresponsive to a high dosage of antihistamines and omalizumab.

4.4.3 Anti IL-5

Eosinophils, are considered to have a pivotal role in the pathogenesis of CSU. Many reports have demonstrated elevated numbers of eosinophils in urticarial lesions when compared with normal skin. Their contribution to CSU pathogenesis is probably achieved through interactions with mast cells, the secretion of histamine and other inflammatory mediators and the activation of the coagulation cascade [70]. The important role of interleukin-5 (IL-5) in eosinophil development and maturation, as well as in increased chemotaxis towards skin urticarial lesions has been well documented [59]. Several monoclonal antibodies were recently approved for the treatment of eosinophil related airway diseases (e.g. asthma, Churg-Strauss syndrome, nasal polyposis etc.) by targeting IL-5 (reslizumab, mepolizumab) or its receptor, IL-5R (benralizumab). These drugs were recently used in three CSU patients who were refractory to classical therapies; two patients responded well and showed a significant improvement with Reslizumab and mepolizumab [71, 72], while the other patient who suffered from symptomatic dermographism (SD) benefited from their treatment with benralizumab [73]. In a recent single-blind, repeated measures study, 12 CSU patients were treated with benralizumab (30 mg subcutaneously) every 4 weeks for 12 weeks following a single dose of a placebo. Among the nine patients who completed the study, five had complete response. Their UAS7 and CU-Q2oL scores improved significantly with benralizumab when compared with the placebo [74]. Gene-expression analysis in patients with CSU following benralizumab treatment demonstrated the normalization of SIGLEC-8 expression and IL-4/5 induced inflammation [75]. Although the results imply that eosinophils play a role in CSU, the exact mechanism of action has not yet been understood. Two clinical trials investigating the efficacy of benralizumab

(NCT03183024) and mepolizumab (NCT03494881) in CSU are still in progress, and their results are not yet available. Regarding benralizumab, a phase IIb study (ARROYO Trial- D3259C00001) is set to start soon.

5. Potential therapeutic approaches

5.1 Eosinophils, mast cells, basophils

5.1.1 Siglec-8

The Siglecs are a family of sialic-acid-binding immunoglobulin-like lectins, which are thought to promote cell–cell interactions and regulate the functions of cells in the innate and adaptive immune systems through glycan recognition. These proteins have regulatory effects on intercellular and intracellular signaling such as the inhibition of cellular proliferation/activation and the induction of apoptosis [76, 77]. Siglec-8 is highly and selectively expressed by eosinophils, but it became clear that it is also expressed by human mast cells and weakly, but consistently, by human basophils. Studies showed that the activation of Siglec-8 induces eosinophil apoptosis (in a caspase-, mitochondrial-, and reactive oxygen species–dependent way). It was also shown that activated eosinophils are especially sensitive to Siglec-8-induced death [78]. It also inhibits the release of FcεRI-mediated histamine and PGD₂ from mast cells [79, 80]. In a recent phase I, randomized, placebo-controlled study conducted with more than 50 healthy volunteers, a single dose of a monoclonal anti-Siglec-8 antibody, namely- AK002 (autolimab) (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, and 1 mg/kg IV), resulted in the complete depletion of circulating eosinophils within one hour from the infusion. This effect was maintained for up to 84 days only in the group who received 1 mg/kg. This result pointed to a possible administration schedule of AK002 at monthly or quarterly intervals [81]. Additionally, in another additional study it was also demonstrated that treatment with AK002 provided symptomatic and histologic improvement in patients with eosinophilic esophagitis [82]. Taking this into consideration, a phase IIa study in CSU and CIndU (cholinergic urticaria and symptomatic dermographism) patients was conducted. These patients received six doses of AK002. At week 22, following treatment, based on changes in UCT score - the response rates in CSU patients were the following, complete + partial response in 92% and 86% in omalizumab-naïve ($n = 14$) and omalizumab refractory ($n = 12$) patients, respectively. In the 12-month open-label extension phase, the response was sustained. No adverse events were observed, with only mild-to-moderate infusion-related reactions recorded [83, 84]. These results suggest that in the future, anti-Siglec-8 antibodies might be a treatment option for CSU patients, who are either omalizumab naïve or refractory to omalizumab.

5.1.2 Other molecules (SHIP-1, PI3K, CD200)

Many new regulatory molecules are recently evaluated for their potential inhibitory effect on mast cell degranulation. Some of them are under development and are to be included in the pipe-line of clinical trials for the treatment of CSU. Among these molecules are SHIP and CD200R, which deserve our attention. It has been shown that SHIP-negative mast cells are more likely to degranulate following IgE binding [85]. The inhibitory effects of SHIP-1 occur through the hydrolysis of phosphatidylinositol 3, 4, 5-trisphosphate by limiting the entry of extracellular calcium, thereby decreasing phosphoinositide 3-kinase (PI3K)-mediated mast cell activation [86–88]. CD200R is a member of the Ig supergene family that is

primarily expressed on myeloid cells. In vivo studies demonstrated that CD200R is an inhibitory receptor that is capable of regulating the activation threshold of inflammatory immune responses. Furthermore, CD200R was also shown to be expressed on mouse and human mast cells and that engagement of CD200R by agonist Abs or ligand results in a potent inhibition of mast cell degranulation and cytokine secretion responses. The proposed mechanism for that effect was possibly due to the inhibition of FcεRI activation that was observed both in vitro and in vivo. [88] Considering their regulatory functions on mast cells, the use of SHIP, CD200R antibodies, or PI3K inhibitors for the treatment of CSU is of great interest.

5.1.3 Anti-histamine H4 receptor

The emerging field of histamine H4 receptors in allergy and clinical immunology is continuously growing. H4 histamine receptor, is a member of the G protein-coupled receptor superfamily that is largely expressed in haematopoietic cells and plays an increasing role in the regulation of immune responses. H4 receptors modulate eosinophil migration and selective recruitment of mast cells that leads to an increased histamine-release and chronic inflammation. It is also involved in T cell differentiation thereby is involved in many immunomodulatory pathways. The observation that H4 is a histamine receptor on many immune cells shed light on the potential of their targeting in inflammatory disorders, such as allergy, chronic pruritus and autoimmune diseases e.g. CSU [89]. Several ongoing clinical studies currently taking place are aimed at evaluating the beneficial effect of targeting H4 receptors in patients suffering from atopic dermatitis and pruritus (JNJ-7777120, ZPL-3893787). Preliminary results have indicated a significant reduction in histamine-mediated scratch and Th2-induced inflammation in atopic dermatitis [90, 91]. These results are encouraging and indicate the need to further evaluate any potential benefits of these drugs in the treatment of CSU.

5.1.4 Mas-related gene X2

MrgX2 is a member of Mas-related genes that is primarily expressed in human dorsal root ganglia and mast cells and is activated by basic peptides. MrgX2 is a multi-ligand receptor responding to various exogenous and endogenous stimuli. As they are highly expressed on skin mast cells, MRGPRX2 triggers their degranulation and release of pro inflammatory mediators, thus promoting multicellular signaling cascades, such as itch induction and transmission in sensory neurons. The expression of MRGPRX2 by skin mast cells and the levels of the MRGPRX2 agonists (eg, substance P, major basic protein, eosinophil peroxidase) are up-regulated in the serum and skin of patients with inflammatory and pruritic skin diseases, such as CSU and atopic dermatitis. Thus, MRGPRX2 and its agonists might possibly be potential biomarkers for the progression of cutaneous inflammatory diseases and the response to treatment in the future. In addition, they may well represent promising targets for the prevention and treatment of signs and symptoms in patients with skin diseases or drug reactions [92].

6. Anti-IgE, B cells

6.1 Quilizimab

Quilizumab, is another new humanized monoclonal antibody directed specifically against membrane-bound IgE. This molecule was also evaluated for its efficacy

and safety for the treatment of CSU in a phase II trial. Unfortunately, following a 20-week treatment with quilizumab 450 mg or a placebo every 4 weeks, no statistically significant differences were observed in all clinical scores ISS7, HSS7, and UAS7 – between the two groups. Moreover, even in the minimally important difference (MID) range the quilizumab group also failed to attain significant differences. [93]. Thus, further development of quilizumab for CSU was discontinued.

6.2 T cell related therapies

6.2.1 TSLP

The expression of thymic stromal lymphopoietin (TSLP), a promotor of Th2 response, was proven to be increased in patients with CSU, thus making the anti-TSLP monoclonal antibody, tezepelumab, a potential treatment alternative for CSU [94, 95].

6.2.2 Anti-IL-17

The finding of increased blood levels of IL-17 in CSU patients was previously reported to be in association with CSU severity. This encouraged us to assess the status of IL-17 in the skin of CSU patients, thus, demonstrating increased IL-17 expression in CD4+ T cells and mast cells of both lesional and non-lesional skin of severe CSU patients. With this in mind, eight severe CSU patients (refractory to all approved therapies and steroid dependent) were treated with the anti-IL-17A antibody, secukinumab, demonstrating a significant improvement in CSU disease activity and were able to discontinue steroids. Future studies should be planned in order to expand this promising therapeutic approach [16, 96].

7. Summary

The need for new treatments evolve from the fact that 15–20% of severe CSU patients will stay unresponsive to Omalizumab and are defined as being of un-met needs. Thus, a better understanding of the complexity of CSU pathogenesis led to the development of many new treatment options. In this chapter we reviewed the known and the ongoing clinical studies of the new treatments for severe CSU. We expect that some of these strategies will be efficient and will be added to the market of the existing therapies.

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References

- [1] Lapi F, Cassano N, Pegoraro V, Cataldo N, Heiman F, Cricelli I, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. *Br J Dermatol* 2016; 174: 996-1004.
- [2] Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, Panasoff J. Clinical and laboratory parameters in predicting chronic urticarial duration: a prospective study of 139 patients. *Allergy* 2004; 59: 869-73.
- [3] Stepaniuk P, Manstein K, Kanani A. Natural history, prognostic factors and patient perceived response to treatment in chronic spontaneous urticaria. *Allergy Asthma Clin Immunol* 2020; 16: 63.
- [4] Erol K, Ertas SK, Ertas R. Fatigue is common and predicted by female gender and sleep disturbance in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol Pract* 2021; 9: 469-476.
- [5] Staubach P, Dechene M, Metz M, Magerl M, Siebenhaar F, Weller k, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011; 91: 557-61.
- [6] Kolkhir P, Pogorelov D, Olisova O, Maurer M. Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus-a systemic review. *Clin Exp Allergy* 2016; 46: 275-87.
- [7] Ghazanfar MN, Kibsgaard L, Thomsen SF, Vestergaard C. Risk of comorbidities in patients diagnosed with chronic urticaria: A nationwide registry-study. *World Allergy Organ J* 2020; 13: 100097.
- [8] Sanchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F, Gonzalez-Aveledo L. Biomarkers of treatment efficacy in patients with chronic spontaneous urticaria. *Eur Ann Allergy Clin Immunol* 2018; 50: 5-9.
- [9] Kolkhir P, Andre F, Church MK, Metz M. Potential blood biomarkers in chronic spontaneous urticaria. *Clin Exp Allergy* 2017; 47: 19-36.
- [10] Vestergaard C, Toubi E, Maurer M, Triggiani M, Ballmer-Weber B, Marsland A, et al. Treatment of chronic spontaneous urticarial with an inadequate response to H1-antihistamines: an expert opinion. *Eur J Dermatol* 2017; 27: 10-19.
- [11] Mekori YA, Giorno RC, Anderson P, Kohler PF. Lymphocyte subpopulations in the skin of patients with chronic urticaria. *J Allergy Clin Immunol* 1983; 72: 681-84.
- [12] Toubi E, Adir-Shani A, Kessel A, Shmuel Z, Sabo E, Hacham H. Immune aberrations in B and T lymphocytes derived from chronic urticaria patients. *J Clin Immunol* 2000;20(5):371-378.
- [13] Chen Q, Zhong H, Chen WC, Zhai Z, Zhou Z, Song Z, Hao F. Different expression patterns of plasma Th1, Th2, Th17 and Th22-related cytokines correlate with serum auto-reactivity and allergen sensitivity in chronic spontaneous urticaria. *J Eur Acad Dermatol Venerol* 2018; 32: 441-48.
- [14] Feng H, Feng J, Zhang Z, Xu Q, Hu M, Wu Y, Lu Y. Role of IL-9 and IL-10 in the pathogenesis of chronic spontaneous urticarial through the JAK/STAT signaling pathway. *Cell Biochem Fuct* 2020; 38: 480-89.
- [15] Auyeung P, Mittag D, Hodgkin PD, Harrison LC. Autoreactive T cells in chronic spontaneous urticarial target the IgE Fc receptor α subunit. *J Allergy Clin Immunol* 2016; 138:761-68.

- [16] Sabag DA, Matanes L, Bejar J, Sheffer H, Barzilai A, Church MK, et al. Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. *Clin Exp Allergy* 2020; 50: 799-804.
- [17] Bracken SJ, Abraham S, Macleod AS. Autoimmune theories of chronic urticaria. *Front Immunol* 2019; 10:627.
- [18] Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticarial: what we know and what we do not know. *J Allergy Clin Immunol* 2017; 139: 1772-81.
- [19] Altrichter S, Zampeli V, Ellrich A, Zhang Ke, Church MK, Maurer M. IgM and IgA addition to IgG autoantibodies against FcRI are frequent and associated with disease markers of chronic spontaneous urticaria. *Allergy* 2020; doi: 10.1111.
- [20] Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. *Immunol Rev* 2018; 282: 232-47.
- [21] Ferrer M. Immunological events in chronic spontaneous urticaria. *Clin Transl Allergy* 2015; 5:30.
- [22] Altrichter S, Frischbutter S, Fok JS, Kolkhir P, Jiao Q, Skov PS, et al. The role of eosinophils in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2020; doi: 10.1016.
- [23] Guillen-Aguinaga S, Jauregui P, Auinaga-Ontoso E, Guillen-Grima F, Ferre M. Up dosing nonsedating antihistamines in patients with chronic spontaneous urticarial: a systemic review and meta-analysis. *Br J Dermatol* 2016; 175: 1153-65.
- [24] Fradin MS, Ellis CN, Goldfarb MT, Voorhees JJ. Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. *J Am Acad Dermatol* 1991; 25: 1065-7.
- [25] Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporine A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997; 52: 312-6.
- [26] Vena GA, Cassano N, Colombo D, Peruzzi E, Piggato P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006; 55: 705-9.
- [27] Kulthanan K, Chaweekulrat P, Komoltri C, Hunnangkul S, Tuchinda P, Chularojanamontri L, Maurer M. Cyclosporine for chronic spontaneous urticaria: A meta-analysis and systemic review. *J Allergy Clin Immunol Pract* 2018; 6: 586-99.
- [28] Kulthanan K, Subchookul C, Hunnangkul S, Chularojanamontri L, Tuchinda P. Factors predicting the response to cyclosporine treatment in patients with chronic spontaneous urticaria: a systemic review. *Allergy Asthma Immunol Res* 2019; 11: 736-55.
- [29] Saini SS, Bindslev-Jensen C, Maurer M, Grob LJ, Baskan EB, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticarial who remain symptomatic on H1 anti-histamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015; 135: 67-75.
- [30] Zuberbier T, Aberer W, Asero R, Abdol-Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA2LEN/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018; 73: 1393-1414.
- [31] Chang TW, Chen C, Lin CJ, Metz M, Church MK, Maurer M. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015; 135: 337-42.

- [32] Magen E, Chikovani T, Waitman DA, Kahan N. Factors related to omalizumab resistance in chronic spontaneous urticaria. *Allergy Asthma Proc* 2019; 40: 273-78.
- [33] Metz M, Vadasz Z, Kocaturk E, Gimenez-Arnau AMK. Omalizumab up dosing in chronic spontaneous urticarial: an overview of real world evidence. *Clin Rev Allergy Immunol* 2020; 59: 38-45.
- [34] Gasser P, Tarchevskaya SS, Guntern P, Brigger D, Ruppli R, Zbären N, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun.* 2020;11:165.
- [35] Arm JP, Bottoli I, Skerjanec A, Floch D, Groenewegen A, Maahs S, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allergy.* 2014;44:1371-85.
- [36] Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med.* 2019;381:1321-32.
- [37] Soong W, Bernstein J, Sussman G, Lanier B, Sitz K, Maurer M, et al. Long-term treatment with ligelizumab achieves prolonged symptom control during the post-treatment follow-up. *J Allergy Clin Immunol.* 2020;145:AB341.
- [38] Sitz K, Soong W, Lanier B, Kobayashi K, Barve A, Hua E, et al. P153 ligelizumab reduces rescue medication use in patients with chronic spontaneous urticaria: phase 2b study results. *Ann Allergy Asthma Immunol.* 2019;123:S28.
- [39] Soong W, Lanier B, Sitz K, Kobayashi K, Barve A, Hua E, et al. P151 ligelizumab achieves sustained control of angioedema in patients with chronic spontaneous urticaria. *Ann Allergy Asthma Immunol.* 2019;123:S27.
- [40] Giménez-Arnau A M., Salman A. Targeted Therapy for Chronic Spontaneous Urticaria: Rationale and Recent Progress. *Drugs* 2020;80: 1617-1634.
- [41] Cohen S, Tuckwell K, Katsumoto TR, Zhao R, Galanter J, Lee C, et al. Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II Trial (ANDES Study). *Arthritis Rheumatol.* 2020. <https://doi.org/10.1002/art.41275>.
- [42] Angst D, Gessier F, Janser P, Vulpetti A, Wälchli R, Beerli C, et al. Discovery of LOU064 (Remibrutinib), a potent and highly selective covalent inhibitor of Bruton's Tyrosine Kinase. *J Med Chem.* 2020;63:5102-18.
- [43] Wedi B. Bruton tyrosine kinase inhibition in dermatology and allergology. *Hautarzt.* 2018;69:519-22.
- [44] Smiljkovic D, Blatt K, Stefanzl G, Dorofeeva Y, Skrabs C, Focke-Tejkl M, et al. BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. *Allergy.* 2017;72: 1666-76.
- [45] Gabizon R, London N. A fast and clean BTK inhibitor. *J Med Chem.* 2020;63:5100-1.
- [46] Marshall MJE, Stopforth RJ, Cragg MS. Therapeutic antibodies: what have we learnt from targeting CD20 and where are we going? *Front Immunol.* 2017;8:1245.
- [47] Mallipeddi R, Grattan CEH. Lack of response of severe steroid dependent chronic urticaria to rituximab. *Clin Exp Dermatol.* 2007;32:333-4.
- [48] Arkwright PD. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. *J Allergy Clin Immunol.* 2009;123:510-1.
- [49] Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory

chronic autoimmune urticaria caused by IgE receptor autoantibodies. *J Allergy Clin Immunol.* 2011;128:1354-5.

[50] Steinweg S, Gaspari A. Rituximab for the treatment of recalcitrant chronic autoimmune urticaria. *J Drugs Dermatol.* 2015;14:1387.

[51] Combalia A, Losno RA, Prieto-González S, Mascaró JM. Rituximab in refractory chronic spontaneous urticaria: an encouraging therapeutic approach. *Skin Pharmacol Physiol.* 2018;31:184-7.

[52] Oliver ET, Chichester K, Devine K, Sterba PM, Wegner C, Vonakis BM, et al. Effects of an oral CRTh2 antagonist (AZD1981) on eosinophil activity and symptoms in chronic spontaneous urticaria. *Int Arch Allergy Immunol.* 2019;179:21-30.

[53] Palikhe NS, Kim SH, Ye YM, Hur GY, Cho BY, Park HS. Association of CRTH2 gene polymorphisms with the required dose of antihistamines in patients with chronic urticaria. *Pharmacogenomics.* 2009;10:375-83.

[54] Oliver ET, Sterba PM, Devine K, Vonakis BM, Saini SS. Altered expression of chemoattractant receptor-homologous molecule expressed on TH2 cells on blood basophils and eosinophils in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2016; 137(304-306):e1.

[55] Altman K, Chang C. Pathogenic intracellular and autoimmune mechanisms in urticaria and angioedema. *Clin Rev Allergy Immunol.* 2013;45: 47-62.

[56] Rossi A, Herlaar E, Braselmann S, Huynh S, Taylor V, Frances R, et al. Identification of the Syk kinase inhibitor R112 by a human mast cell screen [Internet]. *J Allergy Clin Immunol* 2006;118:749-55.

[57] Ramirez Molina C, Falkencrone S, Skov PS, Hooper-Greenhill E, Barker M, Dickson MC. GSK2646264, a spleen tyrosine kinase inhibitor, attenuates the release of histamine in ex vivo human skin. *Br J Pharmacol.* 2019;176:1135-42.

[58] Saini SS, Paterniti M, Vasagar K, Gibbons SP Jr, Patricia M, Vonakis BM. Cultured peripheral blood mast cells from chronic idiopathic urticaria patients spontaneously degranulate upon IgE sensitization: relationship to expression of Syk and SHIP-2. *Clin Immunol.* 2009;132:342-8.

[59] Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β , and TNF- α : receptors, functions, and roles in diseases. *J Allergy Clin Immunol.* 2016;138:984-1010.

[60] Wang D, Duncan B, Li X, Shi J. The role of NLRP3 inflammasome in infection-related, immune-mediated and autoimmune skin diseases. *J Dermatol Sci.* 2020;98:146-51.

[61] Krause K, Metz M, Makris M, Zuberbier T, Maurer M. The role of interleukin-1 in allergy-related disorders. *Curr Opin Allergy Clin Immunol.* 2012;12:477-84.

[62] Federici S, Martini A, Gattorno M. The central role of anti-IL-1 blockade in the treatment of monogenic and multi-factorial autoinflammatory diseases. *Front Immunol.* 2013;4:351.

[63] Krause K, Mahamed A, Weller K, Metz M, Zuberbier T, Maurer M. Efficacy and safety of canakinumab in urticarial vasculitis: an open-label study. *J Allergy Clin Immunol.* 2013;132:751-4.

[64] Néel A, Henry B, Barbarot S, Masseau A, Perrin F, Bernier C, et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome:

A french multicenter study. *Autoimmun Rev.* 2014;13:1035-41.

[65] Bodar EJ, Simon A, De Visser M, Van Der Meer JWM. Complete remission of severe idiopathic cold urticaria on interleukin-1 receptor antagonist (anakinra). *Neth J Med.* 2009;67:302-5.

[66] Assrawi E, Louvrier C, Lepelletier C, Georgin-Lavialle S, Bouaziz JD, Awad F, et al. Somatic mosaic NLRP3 mutations and inflammasome activation in late-onset chronic urticaria. *J Invest Dermatol.* 2020;140:791-8.

[67] Hendricks AJ, Yosipovitch G, Shi VY. Dupilumab use in dermatologic conditions beyond atopic dermatitis—a systematic review. *J Dermatolog Treat.* 2019 (ahead of print).

[68] Ferrer M, Luquin E, Sanchez-Ibarrola A, Moreno C, Sanz ML, Kaplan AP. Secretion of cytokines, histamine and leukotrienes in chronic urticaria. *Int Arch Allergy Immunol.* 2002;129:254-60.

[69] Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *J Allergy Clin Immunol Pract.* 2019;7(1659-1661):e1.

[70] Altrichter S, Frischbutter S, Fok JS, Kolkhir P, Jiao Q, Skov PS, et al. The role of eosinophils in chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2020 (ahead of print).

[71] Maurer M, Altrichter S, Metz M, Zuberbier T, Church MK, Bergmann KC. Benefit from reslizumab treatment in a patient with chronic spontaneous urticaria and cold urticaria. *J Eur Acad Dermatol Venereol.* 2018;32:e112–e11313.

[72] Magerl M, Terhorst D, Metz M, Altrichter S, Zuberbier T, Maurer M, et al. Benefit of mepolizumab treatment in a patient with chronic spontaneous urticaria. *J Dtsch Dermatol Ges.* 2018; 16:477-8.

[73] Bergmann KC, Altrichter S, Maurer M. Benefit of benralizumab treatment in a patient with chronic symptomatic dermatographism. *J Eur Acad Dermatol Venereol.* 2019;33: e413–e415415.

[74] Singh U, Bernstein J. Clinical efficacy of benralizumab and its role in modifying mechanistic pathways in chronic idiopathic urticaria refractory to H1-antagonists. *J Allergy Clin Immunol.* 2020;145:AB249.

[75] Singh U, Bernstein J. Demonstrating clinical efficacy of benralizumab in chronic spontaneous urticaria via normalization of gene-expression in biological samples. *J Allergy Clin Immunol.* 2020;145:AB340.

[76] Crocker PR, Paulson JC, Varki A. Siglecs and their roles in the immune system. *Nat Rev Immunol.* 2007;7:255-66.

[77] O'Sullivan JA, Chang AT, Youngblood BA, Bochner BS. Eosinophil and mast cell Siglecs: from biology to drug target. *J Leukoc Biol.* 2020;108: 73-81.

[78] von Gunten S, Bochner BS. Basic and clinical immunology of Siglecs. *Ann N Y Acad Sci.* 2008;1143:61-82.

[79] Bochner BS. Siglec-8 on human eosinophils and mast cells, and Siglec-F on murine eosinophils, are functionally related inhibitory receptors. *Clin Exp Allergy.* 2009;39:317-24.

[80] Kiwamoto T, Kawasaki N, Paulson J, Bochner B. Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. *Pharmacol Ther.* 2012;135: 327-36.

[81] Rasmussen HS, Chang AT, Tomasevic N, Bebbington C. A randomized, double-blind, placebo-controlled, ascending dose Phase 1 study of AK002, a novel Siglec-8 selective monoclonal antibody, in

healthy subjects. *J Allergy Clin Immunol.* 2018;141:AB403.

[82] Hirano I, Peterson K, Murray J, Dellon E, Falk G, Gonsalves N, et al. AK002, an Anti-Siglec-8 antibody, depletes tissue eosinophils and improves dysphagia symptoms in patients with eosinophilic esophagitis. *J Allergy Clin Immunol.* 2020;145:AB167.

[83] Altrichter S, Staubach P, Pasha M, Rasmussen H, Singh B, Chang A, et al. P152 clinical activity of Ak002, an anti-siglec-8 antibody, in multiple forms of uncontrolled chronic urticaria. *Ann Allergy Asthma Immunol.* 2019;123: S27–S2828.

[84] Altrichter S, Staubach P, Pasha M, Rasmussen H, Singh B, Chang A, et al. Clinical activity of AK002, an anti-siglec-8 monoclonal antibody, in treatment-refractory chronic urticaria. *J Allergy Clin Immunol.* 2020;145:AB239.

[85] 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;95:11330-5.

[86] Gimborn K, Lessmann E, Kuppig S, Krystal G, Huber M. SHIP down-regulates FcεR1-induced degranulation at supraoptimal IgE or antigen levels. *J Immunol.* 2005;136:4565-72.

[87] Kim M-S, Rådinger M, Gilfillan AM. The multiple roles of phosphoinositide 3-kinase in mast cell biology. *Trends Immunol.* 2008;29:493-501.

[88] Cherwinski HM, Murphy CA, Joyce BL, Bigler ME, Song YS, Zurawski SM, et al. The CD200 receptor is a novel and potent regulator of murine and human mast cell function. *J Immunol.* 2005;174:1348-56.

[89] Zampeli E, Tiligada E. The role of histamine H 4 receptor in immune and

inflammatory disorders. *Br J Pharmacol.* 2009;157:24-33.

[90] 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; 130:1023-33.

[91] Thurmond RL. The histamine H4 receptor: from orphan to the clinic. *Front Pharmacol.* 2015;6:1-11.

[92] Fujisawa D, Kashiwakura J-I, Kita H, Kikukawa Y, Fujitani Y, Sasaki-Sakamoto T, 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(622-633):e9.

[93] Harris JM, Cabanski CR, Scheerens H, Samineni D, Bradley MS, Cochran C, et al. A randomized trial of quilizumab in adults with refractory chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2016;138:1730-2.

[94] Kay AB, Clark P, Maurer M, Ying S. Elevations in T-helper- 2-initiating cytokines (interleukin-33, interleukin-25 and thymic stromal lymphopoietin) in lesional skin from chronic spontaneous ('idiopathic') urticaria. *Br J Dermatol.* 2015;172:1294-302.

[95] Takai T. TSLP expression: cellular sources, triggers, and regulatory mechanisms. *Allergol Int.* 2012;61:3-17.

[96] Toubi E, Vadasz Z. The Emerging Role of IL-17 in the Immune-Pathogenesis of Chronic Spontaneous Urticaria. *Immunotargets Ther.* 2020 Oct 22;9: 217-223. doi: 10.2147/ITT.S266410. eCollection 2020.