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Review

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Emerging Therapies in Chronic Spontaneous Urticaria

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ABSTRACT

Chronic spontaneous urticaria (CSU) is characterized by typically short-lived and fleeting wheals, angioedema or both, which occur spontaneously and persist for longer than 6 weeks. This term is applied to the most common subtype of chronic urticaria. The underlying pathophysiology for CSU involves mast cell and basophil degranulation with release of histamine, leukotrienes, prostaglandins and other inflammatory mediators. Although a variety of treatments exist, many patients do not tolerate or benefit from the existing therapies and even require more effective treatments. Omalizumab is currently the only licensed biologic for antihistamine-refractory CSU, and novel drugs are under development. This article reviews its current status regarding pathogenesis and approach to treatment as well as therapeutic agents that are under development for the treatment of CSU.

Keywords: Chronic urticaria; pathophysiology; biologics

INTRODUCTION

Chronic urticaria (CU) is characterized by wheals, angioedema or both for longer than 6 weeks. CU can be further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). CSU is defined by the absence of a specific trigger to skin lesions, whereas CIndU indicates that lesions are activated by a specific stimulus (*e.g.*, symptomatic dermographism, cold urticaria, delayed pressure urticaria, solarurticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria or aquagenic urticarial).[1] The annual prevalence of CU is 0.5% to 2.3%, and its lifetime prevalence is 1.8% across several countries.[2-5] CU has a negative impact on patients' quality of life, with the presence of angioedema often leading to further impairment.[6,7] About 40% of patients with CSU have episodes of angioedema or deeper swelling of dermal or mucosal tissues, whereas 10% have angioedema as their primary manifestation.[8] CU is a self-limited disorder in most cases, with an average duration of 2 to 5 years.[9] In patients in whom no trigger is identified, a rate of spontaneous remission at 1 year is approximately 30% to 50%.[10,11] However, 20% of the patients suffer from CU for more than 5 years.[12]

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In this article, we will focus on treatment targets and new therapies that are in use or under investigation for the treatment of CSU.

PATHOPHYSIOLOGY

Understanding the pathophysiology of CSU is important for identifying potential targets for new therapies. The underlying pathophysiology of CSU involves mast cell and basophil degranulation with release of histamine, leukotrienes, prostaglandins (PGs) and different inflammatory mediators. Mast cell mediators other than histamine (platelet-activating factor, leukotrienes, PGs and cytokines) can also be involved and pronounced cellular infiltrates, including basophils, lymphocytes and eosinophils, are observed.[13] The wheal is characterized by edema, mast cell degranulation and a perivascular mixed infiltrate composed of predominantly CD4+ lymphocytes, monocytes, neutrophils, eosinophils and basophils, similar to an allergen-mediated late-phase reactions.[14] The cytokine profile is characterized by increases in interleukin (IL)-4, IL-5 and interferon-gamma, which is suggestive of a mixed type 1 T helper (Th1)/type 2 T helper (Th2) response.[14-16] Cytokines, which promote a Th2 profile of inflammation (IL-33, IL-25 and thymic stromal lymphopoietin), are increased in the dermis of lesional skin, but not non-lesional skin.[17] Compared to healthy skin, vascular markers and eosinophil/neutrophil infiltration are increased in lesional skin, whereas eosinophils and microvascular changes are also present in uninvolved skin.[18]

Mast cells

Mast cells are derived from bone marrow CD34+, CD117+ (Kit), CD13+ pluripotent progenitor cells that mature under the local environment of the tissues into which they migrate.[19] Immunological staining of tissues have revealed 2 types of human mast cells characterized by their neutral protease content: mast cells which are tryptase-positive but chymase-negative (MC_T) and mast cells which are both tryptase- and chymase-positive (MC_{TC}).[20] MC_T are found typically at mucosal tissues, such as the intestine, lung and nose, are T-lymphocyte dependent and are increased in number in allergic disease.[21] In contrast, the development of MC_{TC} is independent of lymphocytes and they are located primarily in the skin and gastrointestinal submucosa.[22] MC_{TC} account for more than 99% of the mast cells in the dermis of both lesional skin and non-lesional skin of patients with CSU.[22] There are mixed data as to whether skin mast cell numbers are increased in CSU skin. Some studies show increased mast cell number in CSU patients,[15,18,23] whereas others do not find an increase in mast cells in either lesional or non-lesional skin in comparison to the skin of healthy control subjects.[22,24,25] Total serum tryptase levels, an indirect measure of total body mast cell number, are slightly elevated in subjects with CSU compared to both healthy and atopic subjects, but are still within the normal range.[26] However, CSU patients reporting extracutaneous symptoms along with hives have higher tryptase levels than those with only cutaneous symptoms.[27] Mast cell releasability, as assessed by compound 48/80-induced histamine responses via skin chambers, has been shown to be increased in patients with CSU as compared to healthy controls and this enhanced releasability resolves with CSU remission.[24,28]

Immunoglobulin E (IgE)-dependent stimulation leads to degranulation of both subtypes, but MC_{TC} can also be activated by IgE-independent mechanisms. Recently, levels of Mas-related gene X2, a novel G protein-coupled receptor expressed on human mast cells that binds basic proteins, including compound 48/80, are known to be increased in the skin mast cells of

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patients with CSU.[25,29] It has also been noted that CD34+ culture-derived mast cells of subjects with CSU spontaneously release histamine upon sensitization by IgE.[30]

Basophils

Basophils also appear to be involved in the pathogenesis of CSU. Basophils have IgE receptors and are able to produce histamine and cytokines, such as IL-4, IL-13 and IL-31, in response to IgE-receptor activation.[31,32] A unique feature noted in patients with active CSU is that an inverse correlation between blood basophil number and CSU activity has been reported in several investigations, suggesting that basophils are recruited from the bloodstream into urticarial skin lesions during active CSU disease.[33-36] Another unique feature is that basophils of active CSU patients show alterations in IgE-receptor-mediated histamine degranulation that can be divided into 2 equal subsets: CSU responders (CSU-Rs) and CSU nonresponders (CSU-NRs).[37] CSU-R basophils have a histamine degranulation profile similar to that of healthy subjects, whereas basophils of nonresponding patients do not degranulate to *ex vivo* IgE-receptor activation and possess elevated levels of the IgE-receptor regulating inhibitory phosphatases Src homology 2 domain-containing inositol 5-phosphatase (SHIP)-1 and SHIP-2. These 2 functional phenotypes are stable in active disease, are independent of the presence of autoimmune serum factors and also reflect differences in some clinical features.[38,39] A recent study monitoring CD63 induction after IgE-receptor activation of CSU basophils has confirmed the existence of these 2 functional phenotypes.[40]

Improvements in both basopenia and basophil IgE-receptor abnormalities are seen in natural remission of CSU and point to basophils as an important contributor to disease.[36,39] At present, recruitment pathways for basophils to skin lesions in CSU are unknown, but the prostaglandin D2 (PGD2) pathway via the chemoattractant receptor homologous molecule expressed on the Th2 cell (CRTH2) receptor is implicated.[41] Blood basophil activation in CSU is further supported by elevated activation marker expression that is independent of autoimmune factors.[42,43] Evidence from phase III clinical trials of omalizumab therapy in CSU shows that improvement in basopenia occurred in relation to the degree of clinical improvement and dose of omalizumab.[44] In addition, low levels of baseline IgE and basophil IgE receptors have been linked to poorer response to omalizumab.[45-47] Taken together, these lines of evidence support a role for basophils in CSU disease expression.

Autoimmunity

Autoimmunity is believed to be one of the frequent causes of CSU. Type I (IgE to autoallergens) and Type II (IgG autoantibodies to IgE or high-affinity IgE receptor [FcεRI]) autoimmunity have been implicated in the etiology and pathogenesis of CSU.[48] Recently, a large-scale study screening autoreactive IgE in the serum of patients with CSU identified IL-24 as a common, specific, functional autoantigen of IgE antibodies detected in a majority of CSU serum.[49] Also, higher IgE-anti-IL-24 values were associated with higher disease activity. In addition, the past reports of elevated IgG to thyroid antigens had been forwarded as elevated in subjects with CSU.[50,51] While recent data confirm elevated anti-thyroid peroxidase IgE in CSU, there is also evidence of such IgE antibodies in subjects with autoimmune thyroid disease and healthy controls.[52] The absence of skin symptoms in the latter 2 groups raise concerns of specificity for auto-IgE in CSU disease.

In addition, the persistent presence of autoantigens does not easily explain the waxing and waning nature of skin lesions or the locations of eruptions.[53] The clinical relevance of these autoantibodies remains elusive because current therapies, such as omalizumab, seem to work

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regardless of whether or not patients manifest these autoantibodies.[54-56] According to a recent study, the frequency of functional IgG autoantibodies to IgE or FcεRI in subjects without CSU is near zero, whereas it is only 7% in those with CSU.[57] This study used more stringent criteria than past studies to define sera autoreactivity. This included the use of selective inhibitors of the IgE pathway on donor basophils to verify that CSU serum-induced histamine release was due to functional IgG antibodies as well as test that the CSU serum response was reproducible on multiple donors.

Therapeutics

Symptomatic therapy with H_1-antihistamines is the mainstay of treatment for the vast majority of CU patients. Continuous use of H_1-antihistamines in CU is supported not only by the results of clinical trials, but also by the mechanism of action of these medications. These drugs are inverse agonists with preferential affinity for the inactive state of the histamine H_1-receptor and stabilize it in this conformation, shifting the equilibrium toward the inactive state.[58,59] Current guidelines recommend modern second-generation H_1-antihistamines as a first-line symptomatic treatment for CU and suggest up-dosing second-generation H_1-antihistamines up to 4-fold in patients with CU unresponsive to standard doses.[1,60,61] Almost all guidelines recommend this method.[1,60,61] Clinical studies support this method with higher doses of H_1-antihistamines showing a higher efficacy in many patients.[62-64] A recent meta-analysis confirmed that the rate of response to standard dosages of antihistamines in patients with CSU was 38.6% and that the proportion of nonresponding patients with CSU who responded to up-dosing was 63.2%.[65] It is noteworthy that up-dosing improved mainly pruritus, but not wheal numbers.

In children, although steps 3 and 4 are different for each guideline, expert committees recommend a 4-step therapeutic approach as in adults.[1,60,61] According to the guidelines, standard doses of second-generation H_1-antihistamines are used for first-line treatment, and if they are not effective during the first 2–4 weeks, a second-line treatment is attempted. This involves raising the dose of second-generation H_1-antihistamines 2- to 4-fold (weight and age adjusted).

In the treatment algorithm from the recent European Academy of Allergology and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^{2}LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guideline,[1] H_2-antagonists and leukotriene receptor antagonists are not recommended because of the low level of scientific evidence. Other guidelines still recommend adding H_2-antagonists or leukotriene receptor antagonists for step 2 or 3 therapy because of their safety and marginal efficacy.[56,60,61,66] They suggest a short course of oral corticosteroids in order to control hive exacerbations while attempting to adjust baseline medications intended to prevent recurrences. For acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids is treatment of a maximum of 10 days.[1]

The updated EAACI/GA^{2}LEN/EDF/WAO guideline recommends the use of omalizumab (Xolair; Genentech/Novartis, South San Francisco, CA, USA) for patients unresponsive to H_1-antagonists as step 3 therapy based on well-designed robust double-blind placebo-controlled studies demonstrating its efficacy in CSU.[67-69] Omalizumab binds to free IgE, which reduces free IgE levels and causes FcεRI receptors on basophils and mast cells to be down-regulated.[70,71] The timing for reduction of IgE receptors is much earlier for blood basophils than for skin mast cells. This difference in rates of IgE receptor down-regulation was first noted in allergic patients[71] and has recently been confirmed in subjects with CSU.[72] Potential

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mechanisms for omalizumab benefits in CSU include reducing mast cell releasability, reversing basopenia and improving basophil IgE-receptor function, reducing activity of IgG autoantibodies against FcεRI and IgE, reducing activity of IgE autoantibodies against antigens or autoantigens that have yet to be definitively identified, reducing the activity of intrinsically 'abnormal' IgE, and decreasing *in vitro* coagulation abnormalities associated with disease activity.[36,39,44,72-74] While omalizumab has been shown to markedly improve symptoms of CSU, its mechanism of action is not currently understood.

Novel therapies

Newer agents are emerging that may offer additional alternatives for CSU patients beyond antihistamines and omalizumab.

New anti-IgE

QGE031 (ligelizumab) is a humanized IgG1 monoclonal antibody that binds with higher affinity for the Cε3 domain of IgE. Compared to omalizumab, treatment with ligelizumab provided greater and longer suppression of free IgE, basophil FcεRI and basophil surface IgE.[75] It also showed 6- to 9-fold greater suppression of skin prick test responses to allergen. These data suggest that ligelizumab may be more potent than omalizumab in the treatment of CSU. A multicenter, randomized, double-blind, placebo, active-controlled phase 2b dose-finding study of ligelizumab as add-on therapy to investigate the efficacy and safety in patients with CSU (NCT02477332) has been completed. This study aimed to establish the dose-response relationship of ligelizumab with respect to achievement of complete hive response in week 12 and select an appropriate dose, which is likely to be superior to omalizumab at the highest approved dose (300 mg every 4 weeks). There is also an on-going phase III multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study, which has a 52-week double-blind treatment period, and a 12-week post-treatment follow-up period. (NCT03580356).

Spleen tyrosine kinase inhibitors

Spleen tyrosine kinase (Syk) is an intracellular protein tyrosine kinase involved in the downstream signaling events of several immunoreceptors in a variety of cell types—B lymphocytes, mast cells and macrophages.[76] Targeted immunoreceptors include the FcεRI which is expressed on both mast cells and basophils and is believed to contribute to the pathology of diseases such as CSU, and therefore pharmacological inhibition of this kinase could be of benefit. Syk is a promoter of histamine release and cytokine, leukotriene and PG synthesis, whereas SHIP-1 and SHIP-2 are inhibitors.[77] In cultured MCs from CSU patients that displayed elevated histamine release upon anti-IgE stimulation, SHIP-2 was reduced and Syk was elevated.[30]

A Syk inhibitor (GSK2646264) is under investigation in a cream formulation in a randomized, double-blinded study to assess its safety, tolerability, pharmacodynamics and pharmacokinetics in healthy controls and patients with CSU (NCT02424799). This study was completed in November 2017, but the results have not yet been published. *In vitro*, GSK2646264 demonstrated consistent potency across assays relevant to the mechanism of Syk inhibition and good selectivity over a range of closely related kinases.[78] Recently, in an *ex vivo* human skin study, GSK2646264 administered topically or directly to the dermis blocked histamine release from *in situ* skin mast cells.[79]

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Anti-sialic acid-binding immunoglobulin-like lectin-8

Sialic acid-binding immunoglobulin-like lectins (Siglecs) are a family of glycan-binding inhibitory receptors, and among them Siglec-8 is selectively expressed on human eosinophils, basophils and mast cells.[80] Its activation on eosinophils leads to apoptosis, while on mast cells, its activation leads to inhibition of mediator response.[81] AK002 is a humanized non-fucosylated IgG1 monoclonal antibody directed against Siglec-8. Treatment of healthy subjects showed AK002 (0.1–1.0 mg/kg) rapidly depleted blood eosinophils after a single dose for more than 2 weeks.[82] An open-label, phase 2a, pilot study has evaluated the efficacy and safety of AK002 in patients with antihistamine-resistant CU (NCT03436797). The drug was given as monthly intravenous infusions at up to 3 mg/kg. This study showed 12 of 13 (92%) patients in omalizumab naïve CSU patients and 4 of 11 (36%) in omalizumab-refractory CSU patients achieved a complete response by Urticaria Control Test.[83] The reduction rates of Urticaria Activity Score 7 were 75% and 49%, respectively.

Bruton's tyrosine kinase inhibitors

Bruton's tyrosine kinase (BTK) acts critically in signaling cascades in B-cell antigen receptor activation, in Fc receptor binding of immune complexes in myeloid cells, and some Toll-like receptor signaling events in B cells, myeloid cells and dendritic cells.[84] An oral BTK inhibitor (ibrutinib) was tested for effects on skin test responses and IgE-mediated basophil activation in adults with peanut or tree nut allergy. This study showed ibrutinib therapy can reduce both mast cell and basophil IgE activation within 2 days, but stopping therapy also leads to rapid reversal of inhibition.[85] GDC-0853 (fenebrutinib) is a small, highly selective, orally administered inhibitor of BTK which is now being evaluated in an ongoing phase IIa, multicenter, randomized, double-blind, placebo-controlled pilot study in patients with refractory CSU (NCT03137069). Also, a phase II, multicenter, open-label extension study is now assessing the long-term safety and efficacy of fenebrutinib in participants with CSU who have completed the treatment period in a fenebrutinib CSU parent study (NCT03693625).

Anti-CRTH2

CRTH2 is a PGD2 receptor that has been reported to be overexpressed on eosinophils in patients with CSU.[86] Oliver *et al.*[41] suggested that the PGD2/CRTH2 pathway might be involved in the recruitment of basophils and eosinophils to CSU skin lesions. In contrast to the earlier study, they showed a reduction in CRTH2 levels on both basophils and eosinophils of active CSU patients.

AZD1981 (an oral, potent, selective, reversible antagonist of CRTH2) was investigated in patients with CSU who were refractory to H1-antihistamines.[87] This short, 4-week, placebo-controlled treatment study showed a greater benefit on itch scores compared to hives and provided evidence for the recruitment of eosinophils to the skin via the CRTH2 pathway.

Anti-IL-1

Recent findings suggest that IL-1β not only induces urticarial rashes in autoinflammatory diseases, but also plays a role in other allergy-related diseases such as bronchial asthma, contact hypersensitivity and atopic dermatitis.[88] In addition to the dramatic improvement of urticarial rashes in autoinflammatory syndromes upon IL-1 blocking treatments, IL-1 blocking therapies can also be effective in different types of urticaria including delayed pressure urticaria and cold urticaria.[89,90]

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Table. Novel agents in clinical trials for the management of chronic spontaneous urticaria

Target	Agent	Molecule	Intervention	Clinical trials identifier
IgE	QGE031 (ligelizumab)	Anti-IgE	QGE031 SC every 4 weeks	NCT02477332 NCT02649218 NCT03580356
Mast cell/basophil	GSK2646264	Syk inhibitor	Topical application twice daily	NCT02424799
Mast cell/eosinophil	AK002	Anti-Siglec-8	IV infusions at up to 3 mg/kg, monthly for 6 months	NCT03436797
Mast cell/basophil	GDC-0853 (fenebrutinib)	BTK inhibitor	Various doses orally, twice daily 200 mg orally, twice daily	NCT03137069 NCT03693625
Basophil/eosinophil	AZD1981	CRTH2 antagonist	40 mg orally 3 times daily for 7 days	NCT02031679
IL-1	Canakinumab	Anti-IL-1	150 mg SC	NCT01635127
Eosinophil	Benralizumab	Anti-IL-5Rα	SC once a month for 3 months	NCT03183024
	Mepolizumab	Anti-IL-5	100 mg SC, biweekly for a total of 5 doses	NCT03494881

IgE, immunoglobulin E; SC, subcutaneous; Siglec, sialic acid-binding immunoglobulin-like lectin; IV, intravenous; BTK, Bruton's tyrosine kinase; CRTH2, chemoattractant receptor homologous molecule expressed on Th2 cells; Syk, spleen tyrosine kinase, IL, interleukin.

Clinical trials are being conducted to elucidate the role of IL-1 inhibitors in CSU therapy, including a phase II randomized, double-blind, placebo-controlled, single-center study of canakinumab treatment in adult patients with moderate to severe CSU (NCT01635127).

Anti-IL-5

IL-5 induces the maturation, activation, and recruitment of eosinophils. Magerl *et al.*[91] reported that CSU patients exhibit significantly increased numbers of eosinophils in non-lesional skin as compared to control subjects. However, IL-5 is increased in CSU skin lesions.[18] There has been a recent case report on the successful use of mepolizumab (anti-IL-5 monoclonal antibody) in patient with CSU. The efficacy of benralizumab (anti-IL-5 receptor alpha monoclonal antibody) is now being evaluated in a phase 4 study in CSU patients who are refractory to treatment with H1-antihistamines (NCT03183024). Another study is evaluating the efficacy of 100 mg subcutaneous injections of mepolizumab for a total of 5 doses in CSU patients (NCT03494881).

Table shows potential targets and agents under development for use in the treatment of CSU.

CONCLUSIONS

The development and launch of novel agents for CSU are encouraging for the treatment of patients unresponsive to current treatments. As newer biological agents become available, we need to understand both the target and therapeutic mechanism in order to better select appropriate patients for these therapies. As the era of personalized treatment emerges, the best use for the newer agent will be achieved with a deeper understanding of both the phenotype and endotype of each CSU patient.

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