

REVIEW ARTICLE

Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances

Allen Kaplan¹  | Mark Lebwohl² | Ana M. Giménez-Arnau³  | Michihiro Hide⁴ | April W. Armstrong⁵ | Marcus Maurer^{6,7} 

¹Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

²Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

³Department of Dermatology, Hospital del Mar, Institut Mar D'Investigacions Mèdiques, Universitat Autònoma and Universitat Pompeu Fabra, Barcelona, Spain

⁴Department of Dermatology, Hiroshima Citizens Hospital and Department of Dermatology, Hiroshima University, Hiroshima, Japan

⁵Department of Dermatology, University of Southern California, Los Angeles, California, USA

⁶Institute of Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

⁷Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

Correspondence

Marcus Maurer, Institute of Allergology, Charité—Universitätsmedizin Berlin, Berlin, Germany.

Email: marcus.maurer@charite.de

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Abstract

Chronic spontaneous urticaria (CSU) is a debilitating skin disease characterized by intensely itchy wheals, angioedema, or both. Symptoms recur spontaneously, on a near-daily basis, over >6 weeks; many patients experience flare-ups over several years and, consequently, reduced quality of life. Differences between the inflammatory profiles of the skin of CSU patients (wheals and nonlesional sites) and healthy controls indicate that key drivers such as mast cells, eosinophils, and basophils interact, release vasoactive mediators, and prime the skin, leaving patients predisposed to symptoms. Many cytokines and chemokines involved in these inflammatory networks and their corresponding intracellular signaling cascades have been identified. These insights informed the development of therapies such as omalizumab, dupilumab, and Bruton's tyrosine kinase (BTK) inhibitors, marking a renewed focus on pathogenesis in CSU clinical research. Despite progress, current therapies provide symptomatic control but do not appear to redress the inflammatory balance in the skin permanently. A deeper understanding of CSU pathogenesis will permit a more targeted approach to developing novel treatments with curative intent. Here, we review what is known about the pathogenesis of CSU and consider how this can be used to identify rational targets to improve patient care further.

KEYWORDS

angioedema, dermatology, IgE, mast cells, urticaria

Abbreviations: BTK, Bruton's tyrosine kinase; C5, complement 5; CD, cluster of differentiation; CSU, chronic spontaneous urticaria; ECP, eosinophil cationic protein; FcεRI, high-affinity IgE receptor; Ig, immunoglobulin; IL, interleukin; MC, mast cell; MCP, monocyte chemoattractant protein; MRGPRX2, MAS-related G-protein-coupled receptor-X2; NK, neurokinin; PAR, protease-activated receptor; PGD2, prostaglandin D2; SIGLEC, sialic acid-binding immunoglobulin-type lectin; Syk, spleen tyrosine kinase; Th, T helper; TNF, tumor necrosis factor; TPO, thyroid peroxidase; TSLP, thymic stromal lymphopoietin; UAS7, weekly Urticaria Activity Score.

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1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common and debilitating immunological disease that manifests in the skin and is characterized by intensely itchy recurrent wheals, angioedema, or both.^{1,2} Angioedema is experienced by 40%–50% of patients with CSU.^{3,4} However, around 10% of patients report angioedema as their primary symptom.⁴ It remains unclear whether these patients, and patients who report angioedema as their sole symptom, are suffering from a different disorder with a different pathophysiology⁵ or whether these are different phenotypes of CSU. Symptoms arise independently of external causes, although circumstances such as infection or high levels of stress may exacerbate disease activity.¹ Many patients with CSU experience a prolonged disease course that can last for years,^{6–8} with up to one-fifth of patients experiencing multiple episodes as well as symptom-free intervals.^{7,8} The unpredictable nature of the disease, along with its symptoms and associated comorbidities, has a substantial, detrimental impact on patient's quality of life.^{6,9}

There are no curative treatments for CSU: Approved therapies provide symptomatic control but do not appear to affect the natural course of the disease. The first line of treatment is a second-generation H₁-antihistamine. Antihistamines bind to and stabilize the inactive conformation of the histamine H₁ receptor.¹ Although histamine plays an important role in CSU, it is not the only inflammatory mediator contributing to the underlying pathogenesis. Given this, it is not surprising that up to 61% of patients with CSU are refractory to antihistamine treatment administered at the standard dose. However, further clinical benefit can be obtained by increasing the dose¹⁰ and may then raise the success rate to about 45%–55%, leaving close to half of the patients requiring a different approach. Biologic therapy with the anti-immunoglobulin (Ig)E antibody omalizumab was initially investigated in CSU because of its ability to bind IgE against autoantigens and secondarily down-regulate the IgE receptor^{11–16} and is now an established therapy.^{1,17–19} Despite high reported response rates with omalizumab,²⁰ a material proportion of patients still have an insufficient response to CSU treatment, likely due to the multifaceted nature of CSU pathogenesis. In the observational AWARE study, 29% of 936 patients who were inadequately controlled on standard doses of H₁-antihistamines and were followed up for 2 years showed poor disease control, despite receiving specialist care; 32% of 2727 patients who started the study received omalizumab at some point during follow-up.³

Acknowledgment that the underlying triggers of CSU are internal rather than external calls for a renewed focus on the pathogenesis of this condition. For example, the role of mast cells (MCs) in CSU pathogenesis is well established, although the mechanisms of MC activation have not all been fully characterized.²¹ In addition, basophils resemble MCs in many respects and likely contribute to the disease pathogenesis associated with their recruitment to the skin. Another consideration is the effect of the prominent cellular infiltrate of T cells, B cells, monocytes, and eosinophils on CSU pathogenesis and the contributions of coagulation and complement

cascades. These have not yet been fully characterized, but what is known has been reviewed recently.^{22,23} Overall, a deeper understanding of the pathogenesis of CSU permits a more targeted approach to developing novel treatments with curative intent. In this article, we will review what is known about the pathogenesis of CSU and consider how this evidence can be used to identify rational targets to improve the treatment of patients with CSU further.

2 | METHODS

2.1 | Search strategy and selection criteria

Initial searches were performed in PubMed using search strings based on “chronic spontaneous urticaria” and “pathophysiology.” Searches were extended as needed based on an initial literature review and author expertise, and selected based on relevance.

2.2 | Role of the funding source

Novartis Pharmaceuticals Corporation, East Hanover, NJ, provided support for third-party writing assistance for this manuscript.

3 | CLINICAL AND EXPERIMENTAL FEATURES OF CSU

The major clinical features of CSU are itchy wheals and angioedema, which recur spontaneously and occur on most days of the week for over 6 weeks (individual wheals can come and go during a single day).¹ The itch, redness, and swelling associated with the clinical features of CSU are caused by the firing of sensory nerves, vasodilation, and increased vascular permeability.⁴ These manifestations are driven by MC degranulation, releasing vasoactive mediators, particularly histamine.⁴ In addition to the presence of MCs, wheal sites are characterized by infiltration of basophils, eosinophils, monocytes, T lymphocytes, and neutrophils; this is reminiscent of a late-phase cutaneous reaction induced by external allergens, and the cytokine profile of the infiltrate is similar, indicating a predominantly T helper (Th) 2 response.²² Unsurprisingly, however, the infiltrate has a mixed inflammatory profile, with Th1/Th17 cells and cytokines also present.^{24–26}

Analysis of gene expression and transcription in nonlesional skin shows important differences between the skin of patients with severe CSU and healthy controls in terms of mediators of epidermal differentiation, inflammation, and dermal repair.²⁷ Perhaps the most obvious of these is that patients with CSU typically exhibit increased numbers of MCs and microvascular changes in nonlesional sites.^{28–30} Biopsies from lesional and nonlesional skin of patients with CSU also reveal infiltration of high numbers of interleukin (IL)-17A expressing cluster of differentiation (CD)4+ T cells, often in close proximity to IL-17A-expressing MCs.²⁵ The sustained presence

of these cells in the skin, and their interaction via cytokines, may act to sensitize the skin in the event of MC activation,²⁸ contributing to repeated flares and the episodic nature of CSU. Increased levels of the inflammatory marker C-reactive protein,^{31,32} IL-6, a key cytokine,^{22,32} and prothrombin fragment 1 + 2, reflecting coagulation enzyme turnover,³² have been reported in the skin of patients with active CSU, all decreasing during remission. Increased expression of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) has also been observed in the skin of patients with CSU compared with nonlesional skin and controls.³³ Mean platelet volume, a biomarker for platelet reactivity, has similarly been correlated with CSU activity.^{31,32} Finally, D-dimer levels are elevated in active CSU, indicating activation of the coagulation and fibrinolytic pathways^{32,34,35} without evident clinical thrombosis (D-dimer levels may also be useful in monitoring response to treatment).³⁶ Together, these observations point toward CSU being an immune-mediated chronic inflammatory disorder, with dysregulated inflammatory cascades that leave patients predisposed to symptom development. Next, we consider what is known about the key players in this inflammatory signaling network (Figure 1).

4 | THE ROLE OF MAST CELLS

Our current evidence base clearly identifies dermal MCs as the major drivers of CSU and also as important targets for the clinical development of novel therapies.³⁷ Since MCs mature in the tissue to which they have migrated, dermal MCs differ from MCs of other organs such as the lung: The MC_{TC} subtype is largely restricted to the skin and gastrointestinal submucosa. Degranulation of dermal MCs can be IgE-dependent or -independent: Dermal MCs also express receptors for C5a (C5aR), neuropeptides (MRGPRX2), as well as those for cytokines (KIT).²¹ These various signaling pathways make dermal MCs susceptible to activation, perhaps making them uniquely sensitive to the skin.

An obvious avenue for clinical development of potential therapies is to deplete MC numbers or prevent MC differentiation, e.g., by targeting KIT.^{37,38} Another area of interest is to target activation of MCs and resultant degranulation, the critical secretory event in symptom initiation (Figures 1 and 2).^{23,39,40} Various other mechanisms also contribute to these features in CSU; these have been partially characterized and remain the subject of investigation.^{4,30}

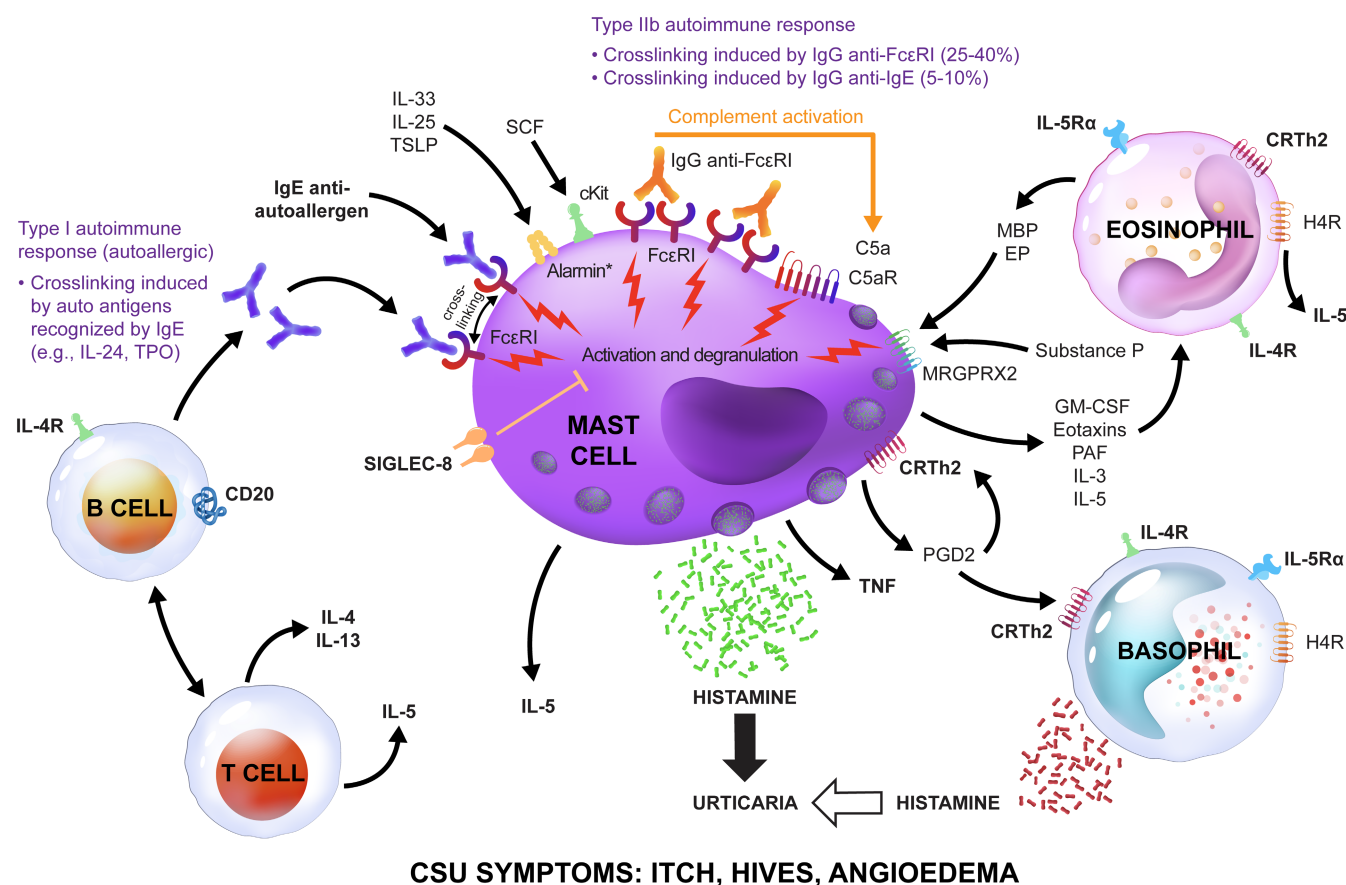


FIGURE 1 Mechanisms of disease: CSU pathophysiology. *Alarmin receptor subunits: IL 33: ST 2/IL1-associated protein. IL 25: IL 17A/IL17 B. TSLP: TSLPR/IL17A. CRTh2—chemoattractant receptor-homologous molecule expressed on Th2 cells; CSU—chronic spontaneous urticaria; C5—complement 5; FcεRI—high-affinity IgE receptor; GM-CSF—granulocyte macrophage colony-stimulating factor; H4R—histamine 4 receptor; Ig—immunoglobulin; IL—interleukin; MBP—myelin basic protein; MRGPRX2—MAS-related G-protein-coupled receptor-X2; NK—neurokinin; PAF—platelet-activating factor; PGD2—prostaglandin D2; SCF—stem cell factor; TNF—tumor necrosis factor; TPO—thyroid peroxidase; TSLP—thymic stromal lymphopoietin.

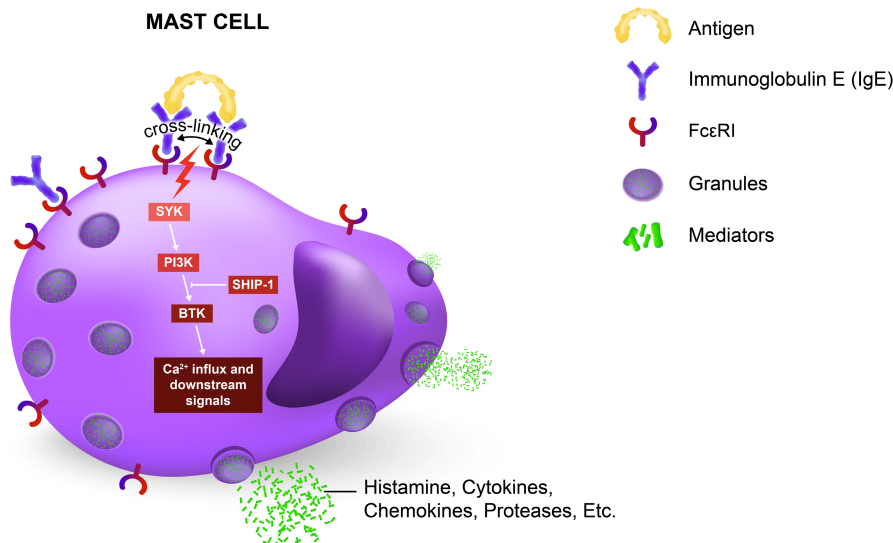


FIGURE 2 Intracellular requirements for mast cell secretion. Increased SHIP-1 in CSU accounts, in part, for the basophil hypo-responsiveness seen with active disease. BTK—Bruton's tyrosine kinase; FcεRI—high-affinity IgE receptor; IgE/G—immunoglobulin E/G; PI3K—phosphatidylinositol 3' kinase; SHIP-1—Src homology domain (SH 2)-containing inositol polyphosphate phosphatase; SYK—spleen-associated tyrosine kinase.

MC activation at the site of wheals is followed by the release of vasoactive mediators into the skin, including histamine, leukotrienes, platelet-activating factor,⁴¹ prostaglandin D2 (PGD2), cytokines and chemokines, and proteases such as chymase and tryptase.^{39,42} These, in turn, promote endothelial cell activation, vasodilation, an increase in vascular permeability, and accumulation of secondary inflammatory cells.^{4,39,42} Together, this cascade results in skin inflammation, edema, and pruritus, which are all major features of CSU.

Cytokines and chemokines amplify the effect of this cascade, promoting further MC activation. Cytokines in lesional skin are broadly similar to those involved in the Th2 response, e.g., IL-4, IL-5, IL-33, IL-25, and TSLP.³³ These are clear targets for future drug development in CSU, with some novel agents already in clinical trials.⁴³ Chemokines derived from MCs and activated endothelial cells promote the recruitment of lymphocytes and eosinophils, among others such as neutrophils and basophils, into the cellular infiltrate around the wheal site.²²

5 | ACTIVATION OF MAST CELLS: CAN IgE UNLOCK THE PATHOGENESIS OF CSU?

Most CSU cases are thought to be due to immunologic mechanisms of MC activation. Two such mechanisms have been described (Figure 1), which most likely contribute to the pathogenesis of CSU in different subpopulations of patients rather than occurring in the same patient, although overlap is possible.^{44,45} Both mechanisms involve the extracellular α -subunit of the high-affinity IgE receptor (FcεRI), which is a predominant part of the receptor that is exposed at the surface of MCs and basophils.^{43,44,46} As an aside, FcεRI may also be relevant in the pathogenesis of chronic inducible urticaria,⁴⁷ though via different triggers to those acting in CSU. Some patients with cold urticaria, symptomatic dermatographism, and solar urticaria have disease that is specifically mediated by IgE, the receptor for which is FcεRI.⁴⁷ However, further exploration of the pathogenesis of chronic inducible urticaria is beyond the scope of this review.

A type I autoimmune response is often characterized as an autoallergic response. The key to autoallergy is the presence of an autoantigen in the skin that can form a complex with IgE and activate MCs. For example, patients develop IgE autoantibodies to autoantigens such as IL-24⁴⁸ or thyroid peroxidase (TPO)¹⁵; these IgE autoantibodies then bind to FcεRI and can be cross-linked if the antigen is present. Patients with CSU have higher levels of IgE-anti-IL-24 (71%) than healthy controls (20%).⁴⁸ Higher IgE-anti-IL-24 levels have also been associated with increased disease activity in patients with CSU.⁴⁸ In addition, the presence of IL-24, which is also involved in autoimmune diseases and skin inflammation,²² has been observed in the skin lesions of patients with CSU, so an *in vivo* contribution is possible.⁴⁹ IL-24 itself can cause basophil or MC degranulation in cells passively sensitized with patient sera, proving that IgE is functional while adding IL-24 to native patient basophils vs. controls has not been assessed.⁴⁸ Similar observations have been made for TPO: Levels of IgE-anti-TPO are increased in CSU compared with healthy controls.^{15,50,51} Patients with CSU, but not healthy controls, show positive reactions to skin prick tests with TPO, and passive transfer of IgE-anti-TPO from a CSU patient to the skin of control subjects who did not exhibit IgE-anti-TPO sensitized the recipient to a positive skin reaction in a skin prick test with TPO.⁵¹ Taken together, these data suggest a pathogenic role of IgE-anti-TPO in CSU. It also appears that the presence of IgE-anti-TPO and IgG-anti-TPO may be linked in CSU: In one study, patients who had IgE-anti-TPO also showed higher IgG-anti-TPO levels compared with patients who did not have IgE-anti-TPO.⁵¹ That said, larger studies with a control population would be welcome to provide more robust support for the autoallergic hypothesis.

A type IIb autoimmune response is one in which IgG and possibly IgM antibodies to FcεRI or IgE cross-link FcεRI or FcεRI-bound IgE, respectively.^{52–54} The incidence of IgG-anti-FcεRI positivity can be as high as 50%. More specifically, sequential determination in large numbers of patients revealed 54 positives out of 104 adult patients,⁵⁵ and 44 positives out of 93 children tested,⁵⁶ with positivity of 52% and 47%, respectively. The main IgG autoantibodies

in play are subtypes IgG1 and IgG3.⁵⁷ These play a dual role in MC and basophil activation since they also fix and activate complement, generating complement 5a (C5a), which binds to its receptor on MCs and basophils and augments histamine release.^{58–60} C5a can be produced by IgG-antigen binding⁵⁸ and by direct cleavage of C5 by coagulation enzymes such as factor Xa. The latter observations, as well as the interactions of C5a-mediated pathways with the protease-activated receptor (PAR) to increase vascular permeability, are areas of active research.⁶¹

The mechanisms of immune dysregulation leading to autoantibody formation in patients with CSU are not known. There is some evidence that the different immunologic mechanisms underlying type I and type IIb CSU give rise to differences in clinical profile, treatment response, and disease activity markers. In particular, type IIb disease comprises a smaller but better-characterized subgroup of patients, more commonly women, who tend to experience high disease activity, poor response to treatment, and comorbid autoimmune disease(s). In the PURIST study, patients with type IIb CSU typically had higher weekly Urticaria Activity Score (UAS7) and showed a trend toward the later onset of disease and higher rates of angioedema compared with patients who did not meet the criteria for type IIb CSU.⁶² Patients with type IIb CSU exhibit a distinct immunological profile from other CSU patients, with key features being low IgE and elevated IgG-anti-TPO.⁶² Observational cohort studies indicate that patients who exhibit immunological features typical of type IIb CSU have a higher risk of developing other autoimmune diseases, particularly Hashimoto's thyroiditis and vitiligo.^{62,63} These autoimmune comorbidities in patients with CSU are also associated with higher rates of hypothyroidism and hyperthyroidism.⁶³ Another interesting finding is that around one-quarter of patients with CSU⁶⁴—compared with ~7% of healthy individuals⁶⁵—exhibit higher-than-expected levels of anti-thyroid autoantibodies, including IgG-anti-TPO and IgG-anti-thyroglobulin, although these features have not yet been linked to a defined clinical profile. As the evidence base linking immunologic and clinical profiles grows, these insights may be used to improve the diagnosis and management of CSU. Endotype-specific treatment approaches would be an important step toward individualized treatment of CSU.

Elevated levels of anti-TPO IgE have been associated with the formation of wheals and have also been identified during skin exacerbations, indicating a role for this antibody in the mechanism underlying disease flares. However, this is not a consistent feature in all patients. It has been suggested that anti-TPO IgE could be a trigger for disease exacerbation, but it is not the only one. Access of thyroid antigen to skin remains to be demonstrated, but a recent study demonstrated that anti-TPO IgE could also bind eosinophil peroxidase.^{66,67} Although not predictive or prognostic in and of itself, elevated serum anti-TPO IgE levels appear to point to CSU predominantly linked to a Th2 response, with higher rates of atopy, asthma, and higher levels of total IgE.⁶⁶

Since IgE also acts as a regulator for FcεRI expression, it is clear from the above mechanisms of MC activation that targeting the IgE

pathway is a promising avenue for research into CSU treatment.⁶⁸ The role of IgE in CSU is likely to be multifaceted since it can also bind to a second receptor: FcεRII (preferred name CD23).⁴⁶ CD23 plays an important role in IgE-facilitated antigen presentation to immune effector cells⁴⁶ during the re-exposure phase of allergic inflammation in the skin. CD23 is also thought to be involved in the regulation of IgE production.⁴⁶ Consideration of the interaction of IgE with its receptors has been especially pertinent in the development of anti-IgE antibodies for the treatment of CSU.

6 | TARGETING IgE: OMALIZUMAB AND LIGELIZUMAB

Omalizumab and ligelizumab^{19,69,70} are anti-IgE antibodies^{11,19,69,70} that have been studied for safety and efficacy in the treatment of CSU, and omalizumab has been approved and employed as treatment for antihistamine-resistant CSU since 2014. In the first of three phase 3 trials totaling >900 patients, 66% of 79 patients receiving omalizumab at 300mg achieved a UAS7 ≤6 at 12 weeks.¹⁹ A UAS7 of zero was achieved in 44% of patients. The 150mg dose also reached statistical significance but with a lower response rate. The optimal 300mg dose was also studied employing either pruritus or intensity of urticaria as the primary endpoints, and the results were virtually superimposable.¹⁸ In this instance, the UAS7 of ≤6 was 53% and UAS7 of zero was 34% at week 12. Once omalizumab was discontinued after 24 weeks, patients' UAS7 scores, as a group, showed a relapse of CSU. A third study yielded very similar results¹⁷ and all three studies were presented to the US Food and Drug Administration for drug approval. A further clinical trial (*n* = 314) has since shown that increasing the omalizumab dose from 150 to 300mg achieves symptom control in a higher proportion of patients.⁷¹ A comprehensive summary of real-world studies indicates that omalizumab up dosing can improve efficacy and quality of life in patients who were not responding to the standard dose.⁷² A further increase in the dose of omalizumab, or more frequent administration, are off-label of clinical benefit with a good safety profile in a pool of patients with CSU who do not respond to the 300mg dose.^{72–74}

In clinical experience, the timing of clinical responsiveness to omalizumab typically sorts into two groups. For some, within a week of the initial dose, there is a rapid amelioration of symptoms. For others, there is a more gradual improvement of symptoms requiring between two and six doses (from 6 weeks to 6 months), but most responders become evident by the third monthly injection.⁷⁵ Data from 114 patients with CSU who received 300mg omalizumab for 12 weeks indicate that nonresponders had significantly lower IgE levels at baseline compared with responders, and a smaller change in IgE during the first 4 weeks of treatment⁷⁶; these two measures may be potential markers to inform treatment decisions. Another, larger retrospective study (*n* = 340) appears to confirm this, showing a significant difference in IgE levels between responders and nonresponders.⁷⁷ So far, it is harder to predict whether a patient will

be a nonresponder or a slow responder. In one small study ($n = 46$), nonresponders had a lower prevalence of atopic disease than slow responders, but IgE levels at baseline were similar for both groups.⁷⁸

The dramatic improvement in the treatment of CSU due to omalizumab led to further research, the goal of which was the creation of a more efficacious anti-IgE agent. This led to the development of ligelizumab, which differs, mechanistically, in a number of ways. It has a slower dissociation rate from IgE when compared to omalizumab, it forms stable tetramers with IgE in plasma rather than trimers and hexamers,^{70,79} the decrease in circulating free IgE is more prolonged, and inhibition of IgE binding to the alpha subunit of FcεRI is more profound. Further, these two anti-IgEs were shown to bind to different IgE epitopes.⁸⁰ Consequently, omalizumab directly competes with IgE binding to CD23⁷⁰ (FcεRII) to a greater degree than does ligelizumab.

These promising observations were followed up by a clinical study in patients with CSU that included not only a placebo control but a head-to-head comparison with omalizumab. A phase 2b dose-ranging trial suggested the superiority of ligelizumab compared with omalizumab.⁶⁹ Nevertheless, in phase 3 trials in patients with CSU, certain tested doses of ligelizumab demonstrated superiority to the placebo control but with no difference when compared with omalizumab.⁸¹ As a result, further development of ligelizumab in CSU has been halted.

In case studies of patients with CSU, dupilumab, a monoclonal antibody that inhibits signaling via IL-4 and IL-13, has reported efficacy.⁸² In a recently presented Phase 3 study of dupilumab versus placebo in 138 patients with antihistamine-refractory CSU, a significant improvement in weekly itch severity score and UAS7 was reported with dupilumab from baseline to Week 24, and it was generally well tolerated.⁸³ However, a second Phase 3 trial in patients refractory to omalizumab has been announced to be stopped due to futility based on a prespecified interim analysis.^{84,85} IL-4 and IL-13 have a role in IgE synthesis and local effects within the cellular infiltrate. As such, dupilumab likely interferes with IgE production and downregulates the Th2 response.

7 | THE INTERACTION BETWEEN MAST CELLS AND EOSINOPHILS UNCOVERS ADDITIONAL PATHOGENIC MECHANISMS

MCs and eosinophils act in tandem in several different immunologic pathways, including response to external allergens.²³ In these responses, MC activation by IgE is the primary event, with eosinophils acting as secondary effector cells. This is also thought to be the case in CSU, with MC-mediated cytokine release being the trigger for eosinophil infiltration into CSU lesions.²³ In turn, eosinophils produce stem cell factor,⁸⁶ which promotes the proliferation and differentiation of MCs,²³ and may contribute to the persistence of high numbers of MCs at the site of wheals and in nonlesional skin. In patients with CSU, eosinophils persist at higher-than-expected levels in uninvolved skin, where they may prime the skin for further outbreaks.²⁸

Proteins secreted by eosinophils may be easily identified in skin biopsies, even when eosinophils are no longer evident.⁸⁷ Conversely, eosinopenia has been associated with high disease activity and poor response to treatment⁸⁸; it is rare in the overall population but occurs in about 1 of every 10 patients with CSU, particularly those with type IIb autoimmune CSU.⁸⁸

Key drivers of eosinophil mobilization from the blood to the skin are chemokines such as eotaxins 1–3, RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted), monocyte chemoattractant protein (MCP)1, MCP3, and MCP4, and the chemotactic factor PGD2.⁸⁹ CRTh2, the receptor for PGD2 (which is secreted by MCs and monocytes), is also expressed on the surface of eosinophils and is thought to be involved in the recruitment of eosinophils to the skin of patients with CSU; this presents another potential target for therapeutic intervention.⁹⁰

Though not a prominent chemotactic factor, IL-5—produced by Th2 cells or directly by MCs—mobilizes eosinophils from the bone marrow, primes them for responsiveness to chemotactic factors by inducing chemotactic receptors, and is anti-apoptotic, thus increasing the half-life of eosinophils within tissues.^{22,23,91} Targeting IL-5, either directly or via its signaling pathway, may therefore provide additional treatment modalities for CSU. Various reports of the clinical efficacy of mepolizumab⁹² and benralizumab^{93,94} support this approach, with both agents currently undergoing clinical trials in patients with CSU.^{95,96}

Another type of crosstalk appears to occur between activated eosinophils and MCs, with eosinophils secreting proteins that regulate MCs, such as eosinophil cationic protein (ECP), eosinophil peroxidase, and major basic protein.²³ This effect may be magnified by IgE autoantibodies targeting eosinophil protein X/eosinophil derived neurotoxin and ECP, contributing to chronic skin inflammation.⁶⁷ Further, external binding of eosinophil proteins to the MAS-related G-protein-coupled receptor-X2 (MRGPRX2) on MCs can promote degranulation and trigger signaling cascades causing itch induction and transmission.^{23,97} MRGPRX2 is responsive to substance P, a mediator of the “flare” portion of “wheal and flare” reaction, so it is of fundamental importance to hive formation. Indeed, expression of MRGPRX2 on skin MCs is upregulated in severe CSU,⁹⁸ and patients with CSU show increased skin reactivity to MRGPRX2 ligands.⁹⁹ This raises the possibility that compounds targeting MRGPRX2 could dampen MC activity.^{97,98}

Signaling between eosinophils and MCs can also involve the coagulation cascade as an intermediary: Eosinophils produce tissue factor, which promotes the coagulation cascade and thrombin formation, as reviewed in detail elsewhere.¹⁰⁰ Thrombin is part of a signaling pathway that cleaves C5 to produce C5a and increases vascular permeability by interaction with endothelial cell PAR-1.¹⁰⁰ Therapeutic blockade of the C5a receptor axis may warrant clinical investigation in CSU since this relates to activation of the classical complement cascade by IgG-FcεRI cell surface complexes⁶⁰ and direct cleavage of C5 by thrombin, Factor Xa and/or plasmin.⁶¹

Finally, like MCs, eosinophils can be inhibited by cell surface receptors such as sialic acid-binding immunoglobulin-type lectin

TABLE 1 Summary of molecular biomarkers in CSU that have potential for future clinical use, as discussed in the text

	Diagnosis	Disease severity	Response to therapy
Anti-IL-24 IgE	Associated with CSU	Associated with active disease	
Anti-TPO IgE and/or IgG	Elevated levels in serum associated with formation of wheals; mostly linked to CSU with a Th2 response. May be a marker for type IIb CSU	Associated with active disease, exacerbations	
IgG-anti-FcεRI	May be a marker for type IIb CSU ^a	Associated with active disease	Associated with a poor response to treatment
Basopenia	May be a marker for type IIb CSU ^a	Associated with more severe disease	Associated with a poor response to treatment ^a
Eosinopenia	May be a marker for type IIb CSU ^a	Associated with active disease	Associated with a poor response to treatment ^a
IL-6		Increased levels in skin during active disease	
CRP		Increased levels in skin during active disease	Elevated levels linked with poor response to antihistamines; role as a marker for other therapies is unclear ^a
D-dimer		Increased during active disease	Elevated levels linked with poor response to antihistamines; role as a marker for other therapies is unclear ^a
IL-33, IL-35		Increased expression in lesional skin of patients with CSU vs. nonlesional skin/healthy controls	
IL-17		May be associated with increased likelihood of repeated flare-ups	
TSLP		Increased expression in lesional skin of patients with CSU vs. nonlesional skin/healthy controls	
C5a		Elevated levels may be associated with active disease	
IgE	Low levels may be associated with Type IIb CSU ^a		Low levels associated with lower chance of response to omalizumab High levels associated with higher chance of response to omalizumab
FcεRI	Low levels may be associated with Type IIb CSU		Low levels associated with lower chance of response to omalizumab Very low levels are associated with no response to omalizumab

Abbreviations: CSU—chronic spontaneous urticaria; CRP—C-reactive protein; C5—complement 5; FcεRI—high-affinity IgE receptor; IgE/G—immunoglobulin E/G; IL—interleukin; TPO—thyroid peroxidase; TSLP—thymic stromal lymphopoietin.

^aSupplementary information based on review published elsewhere.¹²⁵

(SIGLEC)-8, which is expressed on MCs, eosinophils, and to a lesser extent basophils^{101,102}; its activation on eosinophils results in apoptosis.¹⁰³ Therapies targeting SIGLEC-8 include lirentelimab, a humanized monoclonal antibody currently in clinical development for the treatment of CSU.¹⁰⁴ Preclinical data indicate that lirentelimab

can silence MCs and deplete eosinophils in vitro and ex vivo.¹⁰⁵ This mechanism of action appears to be translating into marked clinical benefit, according to data from a Phase 2 study that included both patients with antihistamine-refractory CSU and patients with inducible urticaria.⁴⁰

8 | PATHOGENIC INTRACELLULAR SIGNALING IN CSU

In MCs, an important element of intracellular signaling is Bruton's tyrosine kinase (BTK), which forms part of the signal transduction downstream from FcεRI and, as such, is an intermediary in MC degranulation.^{106,107} Importantly, BTK is also an intracellular mediator of B-cell receptors¹⁰⁸ of every isotype. As such, it has a role in regulating the synthesis of IgE and IgG. Given this role, inhibition of BTK could potentially have a beneficial clinical effect in type I and type IIb autoimmune CSU. BTK inhibition by fenebrutinib¹⁰⁹ or remibrutinib^{108,110} has the potential to both abrogate MC degranulation induced by FcεRI activation and reduce IgE and IgG production in B cells. Indeed, data from a Phase 2 study support the efficacy of fenebrutinib in patients with CSU,¹¹¹ and early data also show improved efficacy and quality of life in patients with CSU treated with remibrutinib compared with placebo.^{112,113} In a Phase 2b randomized study, all tested doses of remibrutinib provided rapid and significant improvements in the primary endpoint (change in UAS7 from baseline to Week 4) compared with placebo. A reduction in both the signs (hives) and symptoms (itching) of CSU occurred as early as Week 1 and was sustained until the end of treatment at Week 12, and the majority of adverse events were mild or moderate.¹¹⁴

Dysregulation of intracellular signaling, trafficking, and cellular function also play a role in other inflammatory cells involved in CSU pathogenesis, including basophils.^{115–117} Basophils are recruited from the bloodstream to the site of wheals in response to signaling via MCP1, MCP3, MCP4,^{22,118,119} and the PGD2-dependent pathway²²; they share FcεRI with MCs and secrete histamine and leukotriene C₄.¹²⁰ Dysregulation of intracellular signaling in basophils appears to hinge on the spleen tyrosine kinase (Syk), which is recruited to FcεRI and activated after antigen binding, initiating downstream signaling cascades.¹¹⁷ As such, Syk is involved in the regulation of FcεRI and promotes the release of histamine and the synthesis of cytokines and leukotrienes.¹¹⁷ In support of this are data showing that basophils from CSU patients with active disease can be divided into two functional phenotypes,¹²¹ which do not have therapeutic implications per se but do provide some insight into how basophils may modulate response to agents that act via the IgE receptor, resulting in a paradoxical difference in systemic histamine release. These phenotypes vary according to their degranulation profile in response to IgE¹²²: In the responder phenotype, Syk expression is high, and basophils showed similar histamine degranulation to that seen in healthy controls; in the non-responder phenotype, Syk has been dephosphorylated by excess levels of Src homology 2 domain-containing inositol polyphosphate 5-phosphatases, which are negative regulators of FcεRI and consequently decrease histamine degranulation by basophils. Therapeutic targeting of Syk could potentially address a major component of the signaling pathway responsible for activating CSU symptoms, with one early-phase clinical study already published.¹²³

9 | REMAINING QUESTIONS AND FUTURE DIRECTIONS

Recent insights into the pathophysiology of CSU have led to the development of novel therapeutic strategies, with some compounds already undergoing clinical investigation. However, several unanswered questions remain. From a clinical perspective, a key question is which of the potential molecular biomarkers identified through our improved understanding of CSU pathophysiology will prove to be most informative during diagnosis and treatment decision-making (Table 1).

Autoallergy as a viable pathogenic mechanism needs confirmation; further studies regarding specificity for CSU are needed, and the identification of other responsible skin antigens. Further, while IgG-anti-receptor antibodies or anti-IgE antibodies are likely to have pathogenic significance, about half of patients with CSU lack them, and the activation mechanism in patients who lack either of these antibodies is unknown. Specific avenues of investigation are likely to provide helpful insights here. Comparatively little is known about the precise mechanisms underlying angioedema and whether a similar cast of cellular players is involved as in wheals. In addition, studies of chronic MC-mediated angioedema are needed to determine whether it is a separate entity or a subpopulation of patients with CSU and angioedema. Another area of interest is the extent to which MCs and complement interact and how this affects the severity and duration of CSU. Further transcriptomic and genomic profiling, as exemplified in some studies, could present an opportunity to identify people who are predisposed to developing CSU and also for therapeutic modulation of the transcriptome.¹²⁴ The answers to these questions may reveal additional targets for investigational therapies.

Finally, a better understanding of the pathophysiology of CSU will inform phenotype and endotype definitions, which are the basis of biomarker identification and validation in tandem with novel compound development. Our overall aim would be to permit more tailored treatment and assess likely responses so that patients can truly benefit.

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ORCID

Allen Kaplan  <https://orcid.org/0000-0002-6566-4743>

Ana M. Giménez-Arnau  <https://orcid.org/0000-0001-5434-7753>

Marcus Maurer  <https://orcid.org/0000-0002-4121-481X>

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