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Immunological Basis of Chronic Spontaneous Urticaria: Immunoglobulin E and Beyond

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Chronic spontaneous urticaria (CSU) is associated with a substantial disease burden due to its prolonged course and significant impairment of quality of life. The diagnostic process for CSU involves confirming the diagnosis itself and identifying disease phenotypes or endotypes, cofactors, and comorbid conditions, which may affect disease activity and severity. Immunoglobulin E (IgE) and non-IgE-mediated mast cell degranulation are the major pathogenic mechanisms of CSU, where FcεRIα, a high-affinity IgE receptor, is the critical therapeutic target. Although the first-line treatment for CSU is typically second-generation H1-antihistamines, anti-IgE antibodies are recommended for patients who are refractory to up-dosed antihistamines. However, some patients with autoimmune phenotypes show incomplete responses. Recently, dupilumab, an anti-interleukin (IL)-4/IL-13 receptor antibody that inhibits type 2 inflammation, was approved by the US Food and Drug Administration. Patients with autoimmune phenotypes treated with Bruton's tyrosine kinase inhibitors have shown promising efficacy. Additionally, emerging biological agents, such as anti-KIT antibodies targeting mast cell activation and survival, and novel anti-IgE therapies (e.g., YH35324), are currently under investigation and are anticipated to become potential therapeutic options. This review provides an update on the pathogenic mechanisms of CSU, including IgE- and non-IgE-mediated mechanisms, and suggests potential therapeutic targets for improving clinical remission rates.

Key Words: Chronic spontaneous urticaria, mast cell, Fc-epsilon receptor, immunoglobulin E, anti-immunoglobulin E antibodies, autoimmunity

INTRODUCTION

Chronic urticaria (CU) is characterized by recurrent itchy wheals, angioedema (AE), or both for >6 weeks. Although CU is one of the most common and distressing skin conditions, precise data on its prevalence are lacking.[1] In the 1970s, a population-based study reported a prevalence of approximately 0.1% for CU in Sweden.[2] Based on questionnaire survey data, the prevalence of CU has been reported as 0.6% in Spain and 0.8% in Germany since 2000.[3,4] In a nationwide population-based study between 2010 and 2014 in South Korea, the overall prevalence of CU was 2.256 per 100000 person-years.[5] CU prevalence varies depending on the study methodology, population, geographic region, sex, and age; however, the overall prevalence appears to be gradually increasing.[5-7] Additionally, CU significantly impairs quality of life, and is typically characterized by a prolonged disease course lasting several years.[8] The associated healthcare costs are also substantial, underscoring the need for concerted efforts to reduce the disease burden of CU.

CU exhibits a wide and heterogeneous clinical spectrum and can be classified in various ways.[7,8] Most notably, CU is classified into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).[7,9] CSU is more common than CIndU,

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comprising approximately 60%–90% of all patients with CU, and some patients may present with both types simultaneously.[7] CIndU is triggered by specific stimuli and includes subtypes such as symptomatic dermographism, cholinergic urticaria, cold urticaria, and solar urticaria. In contrast, CSU occurs without identifiable external triggers; however, various aggravating factors, such as stress, infections, drugs, and other comorbid conditions, including atopy and allergic diseases, can increase disease activity.[9]

A patient can manifest multiple subtypes of CSU simultaneously. CSU subtypes are commonly based on the type of autoantibodies present, presence of AE, associated comorbidities, and treatment response to different therapies.[10]

CU involves diverse pathophysiological mechanisms depending on the subtype, necessitating individualized treatment strategies. To achieve this, conducting a thorough clinical evaluation at diagnosis is necessary, including a detailed history, assessment of abnormal signs, and appropriate diagnostic tests.[9] This can help identify the underlying pathogenesis, triggering or aggravating factors, and comorbidities, particularly allergic and autoimmune diseases. However, in real-world practice, the clinical features and subtypes of CSU are often not clearly distinguished, and a uniform treatment approach is commonly applied, resulting in inadequate disease control. Therefore, this review aimed to summarize the current understanding of immunopathogenic mechanisms, including immunoglobulin E (IgE)- and non-IgE-mediated mechanisms, and the clinical characteristics of CSU, thereby optimizing treatment strategies including emerging therapeutic options.

PATHOGENESIS: IgE-MEDIATED MECHANISM AND BEYOND

The pathogenesis of CSU is heterogeneous and complex, and is still unclear. Although many cell types are involved in the pathogenesis of CSU, skin mast cells are the most important drivers in CSU.[11] Additionally, the high-affinity IgE receptor, FcεRI, is the most critical receptor involved in mast cell activation. FcεRI is a tetrameric complex comprising an extracellular IgE-binding α-subunit, a tetraspan β subunit, and two disulfide-linked γ subunits.[12] The α subunit binds to IgE, while the β and γ subunits are responsible for intracellular signaling transduction as summarized in Fig. 1. In common allergic diseases, such as allergic rhinitis, allergic asthma, and food allergy, mast cell degranulation occurs when surface FcεRI, which is the extracellular α-subunit, is occupied by allergen-bound specific IgE. Therefore, the high-affinity IgE receptor, FcεRI, is the most critical receptor involved in mast cell activation. Atopy and high IgE are predisposing factors for CSU development and severity, and if IgE is already bound to FcεRIα on mast cells, this could increase their activation.[13] Therefore, control of comorbid allergic disease may improve clinical outcomes in CSU management. Mast cells are activated by two types of autoantibodies: IgE (autoallergic, type I CSU) and IgG (autoimmune, type IIb CSU). IgE autoantibodies are produced against auto-allergens

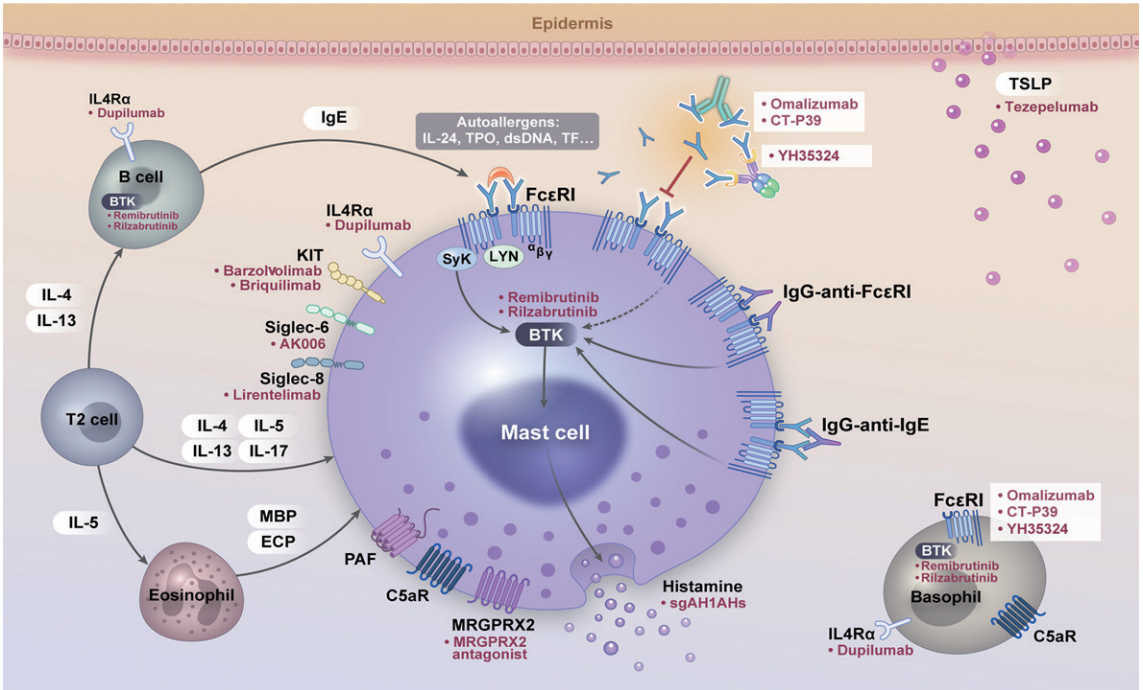

Fig. 1. Mast cell activation mechanisms and therapeutic targets. BTK, Bruton's tyrosine kinase; ECP, eosinophil cationic protein; Ig, immunoglobulin; IL, interleukin; MBP, major basic protein; sgH1AH, second-generation H1 antihistamine; TF, tissue factor; TSLP, thymic stromal lymphopoietin; TPO, thyroid peroxidase.

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such as thyroid peroxidase (TPO), interleukin (IL)-24, double-stranded DNA, tissue factor, and other self-proteins, which could activate mast cells via cross-linking between autoallergen-IgE complexes and FcεRI; IgG autoantibodies against FcεRI, or IgE could activate mast cells via cross-linking between IgG-antigen complex and FcεRI.[11,14,15] Additionally, an overlap of types I and IIb CSU is frequent. Therefore, effective FcεRI suppression could be crucial in CSU management in both IgE-mediated and non-IgE-mediated (types I and IIb) autoimmune phenotypes.

The intracellular signaling pathways involved in mast cells are complex and diverse. Bruton's tyrosine kinase (BTK) functions as a cytoplasmic signaling protein in various immune cells as well as mast cells.[15,16] Upon FcεRI activation, the β and γ subunits are phosphorylated by Lck/Yes-related novel protein tyrosine kinase (LYN), creating docking sites that facilitate the subsequent activation of spleen tyrosine kinase (SYK). After translocation to the cell membrane, BTK is phosphorylated by SYK, which initiates downstream cellular responses. Additionally, BTK regulates intracellular signaling in basophils and B-cells, thereby contributing to cell activation, differentiation, and proliferation. Taken together, BTK represents a potential novel therapeutic target for CSU, although further investigations are needed to determine its positioning.

Mast cells have various receptors on their cell surface that are very sensitive to various stimuli in CSU. The mechanisms of mast cell degranulation independent of FcεRI activation are increasingly being elucidated. Notable alternative pathways include activation of the Mas-related G protein-coupled receptor (MRGPRX2), coagulation cascade activation, complement system activation, and a vicious cycle involving platelet-activating factor (PAF).[17] MRGPRX2 has been identified as a key receptor responsible for non-IgE-mediated anaphylaxis to certain drugs. It can also be activated by endogenous proteins such as substance P, eosinophil cationic protein, major basic protein, and eosinophil-derived neurotoxin. These neuropeptides can be released by stress, defensins, pseudoallergens, and several medications, including neuromuscular blocking agents and fluoroquinolones.[17,18] The MRGPRX2-neuroimmune axis represents an interactive pathway in which psychological stress induces the release of neuropeptides, such as substance P, from peripheral nerve endings, leading to mast cell activation via MRGPRX2 and subsequent induction or exacerbation of urticarial symptoms. Moreover, the interaction between the nervous and immune systems is bidirectional, which may further contribute to persistent pruritus and aggravation of CU symptoms.[19] Coagulation factors, histamine, bradykinin, and PAF can induce vascular leakage directly or via protease-activated receptor 1 (PAR1), which may facilitate the binding of autoantibodies to IgE or FcεRI, and/or the attachment of autoallergens recognized by specific IgE to skin mast cells, ultimately exacerbating urticaria symptoms.[7,17] Additionally, thrombin and factor Xa can directly induce mast cell degranulation through activation of PAR1 and PAR2, respectively. Activated coagulation factors (FXa and FIIa) and plasmin can initiate complement cascades, leading to the production of anaphylatoxins (C3a, C4a, and C5a) and amplification of inflammatory responses. Notably, C3a and C5a can activate mast cells and basophils through their respective receptors, C3aR and C5aR. Skin mast cells are the only mast cell subtype that express C5aR.[16] C5a levels that are elevated in patients with CSU can enhance histamine release induced by IgG-mediated cross-linking of FcεRI.[20]

Although skin mast cells are the key players in CSU, they also interact with other immune cells, thereby contributing to the amplification and chronicity of symptoms.[21] Disease activity and prognosis are influenced by dominant T2 inflammation, autoantibody production by B cells, histamine release from basophils, eosinophil-mediated activation of the extrinsic coagulation pathway, and cellular interactions involving mast cells, eosinophils, and T cells.

DIAGNOSTIC WORK-UP

Confirmation of diagnosis

CSU diagnosis is generally based on characteristic symptoms and signs. However, several other conditions may present with wheals and AE, necessitating a careful differential diagnosis. When wheals are the predominant manifestation of systemic symptoms, such as recurrent unexplained fever, arthralgia, and fatigue, an autoinflammatory disease (e.g., cryopyrin-associated periodic syndromes or the Schnitzler syndrome) should be considered as the primary differential diagnosis.[9,22] If wheals persist for >24 hours and leave bruising or discoloration after resolution, a skin biopsy should be performed to assess for urticarial vasculitis. When AE is the predominant manifestation, bradykinin-induced AE should be considered. A thorough review of a patient's medication history, including the use of angiotensin-converting enzyme inhibitors, is essential to exclude drug-induced AE. Subsequently, hereditary or acquired AE should be evaluated. AE in patients with CSU has a significant negative impact on patient's daily activities and quality of life.[23]

A diagnostic approach to CSU should extend beyond confirming the diagnosis to include identification of underlying causes and endotypes, assessment of symptom-exacerbating cofactors, and evaluation of comorbidities to enable more effective management of symptoms and disease activity (Table 1).[9,22]

Identifying underlying causes of CSU

As discussed in the Pathogenesis section, activation of mast cells in CSU is predominantly mediated through FcεRI. In typical allergic diseases, FcεRI activation occurs when an allergen binds to an IgE that is already bound to FcεRI. Allergens can be classified as exogenous or endogenous, where FcεRI activation

Table 1. Summary of Diagnostic Work-Up for CSU

1. Confirmation of CSU			
presence of wheals and/or angioedema > 6 weeks, without an identifiable external trigger			
2. Identifying underlying causes of CSU			
2-1. Type I - Normal or high serum total IgE - Good response to omalizumab	2-2. Type IIb - Eosinopenia and/or basopenia - Low serum total IgE - Elevated IgG anti-TPO - Positive results of ASST, BAT, IgG-anti-IgE and/or IgG-anti-FcεRI - Poor response to antihistamines and omalizumab	2-3. Mixed - Mixed features of type I and type IIb	2-4. Unknown - Absence of both type I and type IIb features
3. Identification of cofactors affecting disease activity			
3-1. Foods - Pseudo-allergens (preservatives, colorants) - Histamine/salicylate rich foods - Routine avoidance is not recommended	3-2. Drugs - NSAID intolerance - History of urticaria exacerbation after NSAID use	3-3. Stress - History of urticaria exacerbation associated with stress	3-4. Infections - Viral (e.g., HSV-1, HSV-2, EBV, CMV) infection/reactivation - Bacterial (e.g., H. pylori) infection - Parasite infection
4. Identification of comorbidities affecting disease severity			
4-1. CIndU - Dermographism, cold urticaria, cholinergic urticaria are more prevalent - Confirmation of concomitant CIndU via provocation test when necessary	4-2. Autoimmune disease - Hashimoto's thyroiditis is the most common - More prevalent in type IIb CSU	4-3. Mental disorder - Sleep disturbance, anxiety, mood disorders are the most common	4-4. Allergic disease - Allergic diseases (asthma, AD, AR) may be more prevalent in CSU - Elevated serum total IgE - More prevalent in type I CSU

AD, atopic dermatitis; AR, allergic rhinitis; ASST, autologous serum skin test; BAT, basophil activation test; CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; Ig, immunoglobulin; NSAID, non-steroidal anti-inflammatory drug; TPO, thyroid peroxidase.

is primarily driven by endogenous allergens (autoallergens) in CSU.[24] The IgE-Fc portion binds to the FcεRI α-subunit in a 1:1 ratio; however, within the Cε3 region of the IgE-Fc complex, two hydrophobic patches asymmetrically interact with the Ig-like domains of the α-subunit, forming a strong binding reminiscent of two interlocking gears.[24,25] The critical role of the α-subunit in FcεRI-mediated mast cell activation has been demonstrated by the absence of allergic responses in mice lacking the α-subunit.[26] Furthermore, IgG antibodies targeting FcεRI have been identified in patients with CSU. Studies using immunoblotting to detect IgG anti-FcεRIα antibodies reported positive rates in approximately 37%–64% of patients with CSU,[27,28] and among these, 60% of sera were functionally active, inducing histamine release from human basophils.[27] However, serum reactivity against the β- or γ-subunits of the IgE receptor has not been reported.[24] Taken together, these findings indicate that diverse triggers in CSU converge on FcεRI α-subunit activation to initiate mast cell activation, suggesting that therapeutic strategies targeting FcεRI α-subunit may provide broad and effective disease control.

Currently, type I (autoallergic) and IIb (autoimmune) endotypes have been reported in patients with CSU, although 40% of them could not be classified as endotype.[29] Type I is more common (38%–58%) than type IIb (8%); however, the overlap between these two types can occur, with majority of patients with type IIb CSU (approximately 90%) exhibiting type I features.

Identification of type I CSU requires the detection of serum IgE to autoallergens; however, characterization of relevant autoallergens remains limited.[22,29] Currently, the most useful parameter for estimating type I CSU is normal or elevated levels of serum total IgE. Cut-off values for total IgE, defining "high" as above 100 IU/mL and "low" as below 43 IU/mL, have been proposed; however, a consensus on these thresholds has not yet been established. Type I is often associated with concomitant allergic diseases and is characterized by a favorable response to anti-IgE treatment.[11]

In type IIb CSU, elevated C-reactive protein (CRP) levels are more commonly observed, while blood eosinophil and basophil counts are often reduced.[29] Increased levels of anti-TPO-IgG and lower total IgE are frequently detected; the elevated ratio of anti-TPO-IgG to total IgE is considered a useful surrogate marker for type IIb CSU.[9,11,29] Confirming a low total IgE level (<40 IU/mL) together with elevated anti-TPO IgG can be

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useful for identifying type IIb in clinical practice. A positive result on autologous serum skin test, basophil activation test, or basophil histamine release assay, and the presence of IgG autoantibodies to IgE and/or FcεRI can define type IIb CSU[29]; since all three criteria need to be met, the prevalence of type IIb CSU is lower than that of patients with detectable IgG autoantibodies against IgE and/or FcεRI. Furthermore, these assays are not widely used in routine clinical practice. Patients with type IIb CSU have a higher prevalence of comorbid autoimmune diseases and are characterized by a poor response to antihistamines and anti-IgE treatment.[30]

Identification of relevant cofactors and comorbid conditions affecting disease activity

Patients with CU show higher rates of IgE sensitization compared with the general population.[31] In a cross-sectional analysis, comorbid allergic diseases were observed as follows: asthma (10.8%), atopic dermatitis (AD) (9.8%), and allergic rhinitis (3.7%). The rates of comorbid allergic diseases in patients with CSU were higher than those in control individuals.[32] Increased serum total IgE levels have been reported in approximately 18%–82% of patients with CSU, especially in those with AD or type I autoallergy, which were associated with a longer disease duration.[33,34] Taken together, type 2/IgE-mediated responses, observed in atopy or allergic diseases, could contribute to mast cell activation in CSU, and anti-IgE treatment can have greater effectiveness in patients with CSU who have comorbid allergic diseases.

Various cofactors (foods, drugs, stress, and infections) and comorbid conditions may also influence disease activity.[18] Although many patients report a perceived association between certain foods and their symptoms, true food allergy is rarely diagnosed; however, pseudoallergens, such as preservatives and colorants contained in food, may activate mast cells through MRGPRX2.[9,18] Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common medications that exacerbate symptoms in patients with CSU (up to 30%), which is referred to as NSAID-exacerbated cutaneous disease.[10,29] These patients should avoid NSAIDs and instead use selective cyclooxygenase-2 inhibitors.[35] Infections are known to trigger or exacerbate symptoms of urticaria, and an individualized approach is required according to the patient's medical history, symptoms, and condition.

CIndU, autoimmune diseases, allergic diseases, and neuropsychiatric disorders could affect disease severity.[9,36] Patients with concomitant CIndU tend to have a poorer response to antihistamines and a longer disease duration.[36] Autoimmune conditions associated with CSU include autoimmune thyroid disease, pernicious anemia, vitiligo, type 1 diabetes, and rheumatoid arthritis; 28% of patients with CSU have at least one autoimmune disease in type IIb; Hashimoto's thyroiditis was the most common (21%).[37,38] Moreover, the treatment with thyroid hormones has been reported to significantly improve urticaria symptoms in those with autoimmune thyroid disease.[39,40] It is recommended that coexisting autoimmune diseases in CSU should be identified and appropriately managed.

CURRENT AND FUTURE TREATMENT

The goal of CSU treatment is to treat the disease until complete control, defined as the total absence of symptoms during treatment (clinical remission), is achieved.[9,41] Recently, "cure remission" has been proposed to define the total absence of signs or symptoms without any medication.[41] Currently, pharmacological treatments are limited to improving symptoms by suppressing mast cell mediator effects. However, there remains an unmet need for disease-modifying therapies that can inhibit the upstream pathways of mast cell activation, thereby preventing or delaying CSU progression and its associated comorbidities, to achieve clinical remission.[42]

Pharmacologic treatment: antihistamines and immunosuppressive agents

Pharmacological treatment options aim to target mast cell mediators via inhibitory receptors or to reduce the number of mast cells (Fig. 1). The international guidelines suggest a stepwise treatment algorithm including second-generation H1-antihisatmines (sgH1AHs), omalizumab, and cyclosporine.[9] sgH1AHs are recommended as the first-line treatment for symptomatic control, and if not controlled, the dose should be increased to four times the standard dose.[9] Up to 60% of patients with CU showed insufficient response to first-line treatment requiring increased doses.[43,44] A higher serum total IgE level shows a good response to sgH1AHs, while those with lower total IgE or type IIb show poor response.[30,44] Additionally, high disease activity, high levels of CRP and D-dimer, previous treatment with corticosteroids, and concomitant CIndU are associated with poor responses to sgH1AHs.[45]

Cyclosporine, a calcineurin inhibitor, could inhibit mediator release from mast cells.[46] Cyclosporine combined with sgH1AHs was effective for CU control; a meta-analysis reported that 73% of patients responded to low (from 2 to <4 mg/kg/day) to moderate (4–5 mg/kg/day) doses at week 12.[46] Adverse events, including elevated serum creatinine and gastrointestinal symptoms, appear to be dose-dependent and occur in >50% of patients.[46] Therefore, cyclosporine is recommended only for patients refractory to a combination of antihistamines and omalizumab due to its adverse effects. Although other immunosuppressants, such as tacrolimus,[47] mycophenolate,[48] and sirolimus[49] have been used to treat refractory CSU, their roles may be alternative agents to omalizumab and cyclosporine with limited evidence.

Biological agents: anti-IgE and anti-IL-4R/IL-13

Anti-IgE antibody

Omalizumab, a recombinant, humanized anti-IgE, prevents

free IgE from binding to FcεRI and downregulates the number of FcεRI receptors on mast cells or basophils.[50] In 2014, omalizumab was approved for CSU treatment (≥12 years of age at a dose of 300 mg every 4 weeks), and also approved for other allergic diseases including severe asthma, chronic rhinosinusitis with nasal polyps, and food allergy. The international guidelines recommended omalizumab as an add-on treatment in patients with CSU unresponsive to high doses of sgH1AHs.[9] The efficacy and safety of omalizumab have been demonstrated to show a dose-dependent response.[51] However, approximately 30% of patients remain symptomatic at licensed doses over a 6-month period.[52] The updosing of omalizumab (up to 600 mg) provided better symptom control with complete response (up to 60%).[43,53] Low total IgE levels are strong predictors of poor response, whereas >2-fold increase in total IgE within the first 4 weeks may be associated with an improved treatment response.[45,54] Since elevated total IgE levels have been associated with early response,[55] a retrospective cohort study involving 386 patients refractory to sgH1AHs revealed that, in addition to IgE levels, a high initial omalizumab dose (≥300 mg), elevated basophil counts, and a low platelet-to-lymphocyte ratio are predictors for early responses.[55] Patients with type IIb CSU exhibited poor treatment responses, which were associated with autoimmunity-related markers including a positive basophil activation test, basophil histamine release assay, and anti-TPO-IgG.[45] Ligelizumab is an anti-IgE monoclonal antibody similar to omalizumab, but has 50 times higher affinity for IgE.[56] Two phase 3 studies that compared ligelizumab with omalizumab in patients with sgH1AH-refractory CSU could not demonstrate any superiority over omalizumab. CT-P39 (OMLYCLO®) was approved as a biosimilar of reference omalizumab by the European Medicines Agency and the Ministry of Food and Drug Safety of the Republic of Korea.[57,58] The phase 3 trial demonstrated equivalent efficacy and comparable safety between CT-P39 (150 mg/300 mg) and omalizumab (150 mg/300 mg) during 12 weeks of treatment in patients with CSU, demonstrating that CT-P39 can be an effective omalizumab biosimilar.[59]

Anti-IL-4R/IL-13 antibody

Dupilumab is a monoclonal antibody that blocks IL4-Rα, thereby inhibiting both IL-4 and IL-13 signaling. It has been approved for various type 2 inflammatory diseases such as AD, asthma, chronic rhinosinusitis with nasal polyps, prurigo nodularis, and eosinophilic esophagitis. Two phase 3 trials demonstrated efficacy and safety as an add-on to sgH1AHs in refractory patients with CSU who were omalizumab-naïve (CUPID A) and those with intolerant or incomplete response (CUPID B), respectively.[60] Dupilumab reduced the severity of itching and hives with sustained efficacy throughout the off-treatment period compared with placebo in omalizumab-naïve patients. The number of patients in clinical remission was significantly higher after dupilumab treatment (CUPID A). However, dupilumab efficacy was low in omalizumab-intolerant or incomplete responders (CUPID B). Therefore, dupilumab is expected to be particularly beneficial in type I CSU, especially in atopic patients with high IgE levels, eosinophilia, or comorbid asthma and/or AD. In a recent CUPID C study, which was similar to CUPID A, 30% of dupilumab-treated patients achieved a complete response at 24 weeks, similar to the results of CUPID A.[61] Dupilumab showed clinically significant improvements in urticaria disease activity in omalizumab-naïve patients with refractory CSU, and a small improvement in patients who were intolerant or incomplete responders to omalizumab. In 2025, dupilumab has been approved for antihistamine-refractory patients with CSU aged ≥12 years by the US Food and Drug Administration (FDA).

Emerging drugs under investigation

Novel anti-IgE

YH35324, a long-acting IgETrap-Fc fusion protein, consists of the extracellular domain of human FcεRIα and a human IgD/IgG4-modified Fc region, and has enhanced IgE binding affinity compared with omalizumab and a reduced risk of IgG1 Fc-mediated side effects, such as anaphylaxis, which are thought to be associated with Fc gamma receptor activation.[62] YH35324 alleviates food allergy symptoms by reducing mast cell numbers, free IgE levels, and mast cell degranulation in mouse models,[62] and is a novel therapeutic agent being developed for the treatment of various IgE-mediated allergic diseases, including CSU, particularly in patients with extremely high total IgE levels (>700 IU/mL) or high body weight. A phase 1 trial demonstrated greater suppression of serum-free IgE levels over a longer duration in a dose-dependent manner compared with omalizumab in atopic individuals with allergic conditions, including allergic rhinitis, AD, food allergy, urticaria, and healthy controls. It has a favorable safety profile, and no serious adverse events have been reported. A study of YH35324 in 64 individuals with allergic diseases showed more significant FcεRIα suppression on peripheral basophils and IgE-unbound FcεRI expression on the surface of human mast cells compared with omalizumab.[63] These findings suggest that YH35324 has novel anti-IgE immunomodulating effects via suppression of FcεRIα-mediated mast cell activation. A recent phase 1b study of YH35324 (NCT05960708) was performed in patients with CSU refractory to sgH1AHs and omalizumab. Taken together, YH35324 has shown favorable efficacy and safety in patients with CSU, although further evidence is needed to validate its efficacy in phase 2 and 3 trials in patients with CSU and those with autoimmune phenotypes.

BTK inhibitors

BTK is involved in the signal transduction downstream from FcεRI in mast cells/basophils, regulating IgE/IgG synthesis in B cells.[16] BTK inhibition is a promising therapeutic target and

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is expected to be effective in type I and type IIb CSU, the latter being characterized by higher disease activity and reduced responsiveness to omalizumab. Highly selective BTK inhibitors with few adverse effects have been investigated for CSU.[16]

Fenebrutinib is a potent, selective oral BTK inhibitor. In a phase 2 trial among 93 patients with sgH1AHs-refractory CSU, fenebrutinib showed a rapid improvement in disease activity in patients with and without type IIb autoimmunity.[64] However, further development was stopped owing to adverse events (transient transaminase elevations). Two phase 3 trials of remibrutinib, an oral, highly selective BTK inhibitor, were conducted.[65] A total of 470 (REMIX-1) and 455 (REMIX-2) patients with sgH1AHs-refractory CSU (≥18 years old) received remibrutinib (25 mg twice daily) vs. placebo for 24 weeks, during which symptom improvement was significantly greater, and higher complete- and well-controlled rates were noted in the remibrutinib group than in the placebo group. Remibrutinib has recently been approved for CSU by the FDA. Rilzabrutinib is an oral, reversible BTK inhibitor with high-target specificity. A phase 2 trial demonstrated that rilzabrutinib (1200 mg/day) led to significant symptom improvement at week 12, with a rapid onset observed as early as week 1.[66] In subgroup analyses, favorable effects were observed in patients with low IgE and eosinophil levels, a positive basophil histamine release assay result, and AE, suggesting that this treatment may be particularly promising for type IIb patients.

Anti-KIT

Activation of the KIT receptor tyrosine kinase by its ligand stem cell factor is required for the differentiation, chemotaxis, maturation, and survival of mast cells.[67] Barzolvolimab is a potent inhibitor of stem cell factor-dependent KIT activation in skin mast cells, and has demonstrated reductions in itching and urticarial lesions.[68] In a recent phase 1b study, multiple doses of barzolvolimab were well tolerated in 45 patients with CSU, with mild or moderate adverse events that resolved. Rapid symptom reduction within 1 week was observed and sustained for 12 weeks across barzolvolimab doses, regardless of prior omalizumab treatment. A phase 2 study (NCT05368285) confirmed similar efficacy and safety to this study,[69] and two phase-3 studies are currently recruiting patients. Briquilimab, an IgG1 anti-KIT antibody, is currently under clinical investigation in a phase 1b/2a dose escalation study in adult patients with CSU.

MRGPRX2 antagonist

MRGPRX2 has been proposed to play an important role in mast cell-driven diseases, including CSU. Gene expression and serum levels of MRGPRX2 are elevated in patients with CSU and are related to disease severity.[70,71] Thus, MRGPRX2 has emerged as a potential novel drug target for CSU.

Anti-sialic acid-binding immunoglobulin-like lectins (Siglecs)

Sialic acid-binding immunoglobulin-like lectins (Siglecs) are a family of immune regulatory receptors found primarily on immune cells. Siglec-6 and Siglec-8 are inhibitory receptors of mast cells, and monoclonal antibodies against Siglec-6 and Siglec-8 are new candidates for several mast cell-related diseases including CSU.[72] Lirentelimab, an anti-Siglec-8 mAb, selectively inhibits mast cells and depletes eosinophils via apoptosis.[73] In a phase 2a study, complete response rates were 92% and 36% in omalizumab-naïve and -refractory patients, respectively; however, a phase 2 study (NCT05528861) reported a failure to meet the primary endpoints.[73,74] Recently, a phase 1 (NCT06072157) and an open-extension study (NCT06577116) of AK006, an anti-Siglec-6 mAb, in patients with antihistamine-refractory CSU have been completed.

Anti-thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that plays a vital role in type 2 inflammation by activating various cells including mast cells and basophils. Increased serum levels of TSLP were noted in patients with CSU compared with those of controls.[75] A phase 2b study demonstrated no significant symptom improvement at week 16 in 183 patients with CSU with or without omalizumab treatment.[76] Additionally, omalizumab-naïve patients showed a delayed and sustained improvement lasting 32 weeks off treatment, accompanied by decreasing trends in type 2 biomarkers. These trends were more pronounced in patients with lower IgE levels and longer disease durations. Further investigations are required to validate these findings.

CONCLUSION

CSU is a common, long-lasting condition that significantly affects the quality of life. Diagnosis includes identification of endotypes and comorbidities to enable personalized treatment. Mast cell degranulation, particularly via FcεRI, is central to its pathophysiology. Antihistamines and omalizumab are currently the recommended treatments. Novel therapies, including biologics and small molecules targeting mast cells, are currently being studied for CSU. Dupilumab and remibrutinib were recently approved for CSU by the FDA, and other BTK inhibitors have shown good responses. Anti-KIT and MRGPRX2 antagonists are expected to be useful treatment options in the future. Novel anti-IgE, YH35324, which demonstrated greater suppression of FcεRIα-mediated mast cells compared with omalizumab, may be an alternative drug to omalizumab.

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AUTHOR CONTRIBUTIONS

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