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REVIEW

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Current View of Chronic Spontaneous Urticaria

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a disorder that persists for more than six weeks and is not caused by a defined physical stimulus. It can be seen in all age groups, ethnicities, and geographical regions and affects approximately 1% of the population. Current data suggests that CSU is an autoimmune-related disease. Two separate endotypes have been identified based on the character of autoantibodies that play a role in mast cells (MCs) activation. According to the Gell and Coombs hypersensitivity classification, CSU caused by IgE type auto-antibodies is classified as type-I endotype (type-I aiCSU), whereas CSU caused by IgG type autoantibodies is classified as type-IIb endotype (type-IIb aiCSU). While both endotypes exhibit similar phenotypic characteristics, there are clinical differences in disease activity, accompanying comorbidities, and treatment response. The triple positivity of autologous serum skin test (ASST), basophil activation tests (BAT), and IgG type autoantibodies against MCs high-affinity IgE receptor (FcεRI) or IgE is considered in favor of type-IIb aiCSU, while positivity of IgE type autoantibodies suggests type-I aiCSU. The guidelines recommend the use of second generation antihistamines for first-line treatment. Omalizumab, an anti-IgE monoclonal antibody, is a treatment option in cases that do not respond to high-dose antihistamine therapy. Type-IIb aiCSU has a poor response to antihistamines and omalizumab but cyclosporine shows a favorable result in this group. Determination of endotypes in CSU might be an important step for defining of treatment selection. Further studies are needed to reveal more specific biomarkers and to develop new treatment agents.

Keywords: Chronic spontaneous urticaria, type-I chronic spontaneous urticaria, type-IIb chronic spontaneous urticaria, autoimmune urticaria

URTICARIA DEFINITION and CLASSIFICATION

Urticaria is a vascular skin disorder characterized by hives, angioedema (subcutaneous edema), or a combination of both. Hives are superficial and itchy swellings limited to the dermis, and have distinct features such as having various shapes and sizes and sharp borders, being generally surrounded by reflex erythema, and disappearing rapidly (within 30 minutes to 24 hours) without leaving a trace. Angioedema is a deeper form of edema that can occur in the dermis or submucosal tissue, either by itself or in conjunction with hives. Angioedema is swelling in the deep layers of the skin, and unlike hives, the swellings are pale, indistinct, painful rather than itchy, and usually take more than a day (up to 72 hours) to disappear.

Acute urticaria (AU) is defined as disease duration of less than 6 weeks, whereas chronic urticaria (CU) is defined by the presence of urticaria most days of the week, usually for 6 weeks or longer (1). About 40% of patients with CU have episodes of accompanying angioedema, while 10% have angioedema as their sole manifestation (2).

Chronic urticaria is classified into two groups; inducible urticaria if a physical trigger can be identified, and spontaneous or idiopathic urticaria if no triggering factor can be detected (Table I). Although the frequency of CU varies in different societies, it is approximately 1.4% (3). About 20% of CU is inducible urticaria, while in the remaining 80% of the cases there is no external trigger or an identified condition that explains the occurrence of urticaria. It has been shown that inducible urticaria (often

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dermographism) can accompany patients with chronic spontaneous urticaria (CSU) (4). For this reason, the frequency of chronic urticaria subtypes in the population is not known exactly.

URTICARIA PATHOGENESIS

The main mechanism in the formation of urticaria is the activation and degranulation of mast cells (MCs) in the skin. Histamine and other inflammatory mediators (prostaglandins, leukotrienes, cytokines, and kinins) released from the granules cause sensory nerve activation, vasodilation, and plasma extravasation, as well as perivenular infiltration of inflammatory cells. When biopsied from urticarial plaques, a leukocyte infiltrate consisting of T lymphocytes (especially T helper-2), eosinophils, neutrophils, and basophils is observed. These cells can be activated by mediators in the environment and can further activate MCs. While data regarding the roles of eosinophils, lymphocytes, and neutrophils in the pathophysiology of the disease is limited, there is evidence that the administration of steroids during acute treatment contributes to the resolution of urticaria. It is known that steroids do not have an effect on MC activation. They probably exert their effect by inhibiting the chemotactic response in the cellular infiltrate (5). MCs are produced from CD34+, CD117+ (c-kit), and CD13+ pluripotent progenitor stem cells in the bone marrow. There are two different subsets of MCs: MCt (mast cells which are tryptase positive but chymase negative) and MCtc (MCs which are both tryptase and chymase positive). MCt are T-lymphocyte dependent cells identified in mucosal tissues (i.e., intestine, lung, and nose), while MCtc are T-lymphocyte independent cells mainly found in the skin and gastrointestinal submucosa. The MCtc phenotype accounts for over 99% of the MCs in the dermis of both lesioned and non-lesioned skin of patients with CSU. Studies have shown functional differences between MCt and MCtc (6). IgE-dependent stimulation causes degranulation of both MC subtypes (6). However, MCtc can also be activated by IgE-independent mechanisms (6).

Table I: Chronic Urticaria Classification and Subtypes (1).

Chronic Urticaria	
Chronic Spontaneous Urticaria	**Chronic Inducible Urticaria**
• Type-I (auto-allergic) • Type-IIB (autoimmune)	• Symptomatic Dermographism • Cold urticaria • Delayed Pressure Urticaria • Solar Urticaria • Heat Urticaria • Vibratory Angioedema • Cholinergic Urticaria • Contact Urticaria • Aquagenic Urticaria

MCs contain many membrane receptors, including high-affinity IgE (FcεRI), low-affinity IgG (FcγRII/CD23), inhibitory siglec-8, complement 5a (C5a), G protein-coupled receptors (GPCRs), and mas-related G protein-coupled receptor X2 (MRGPRX-2) receptors (Figure 1) (7). They also express neuropeptide receptors

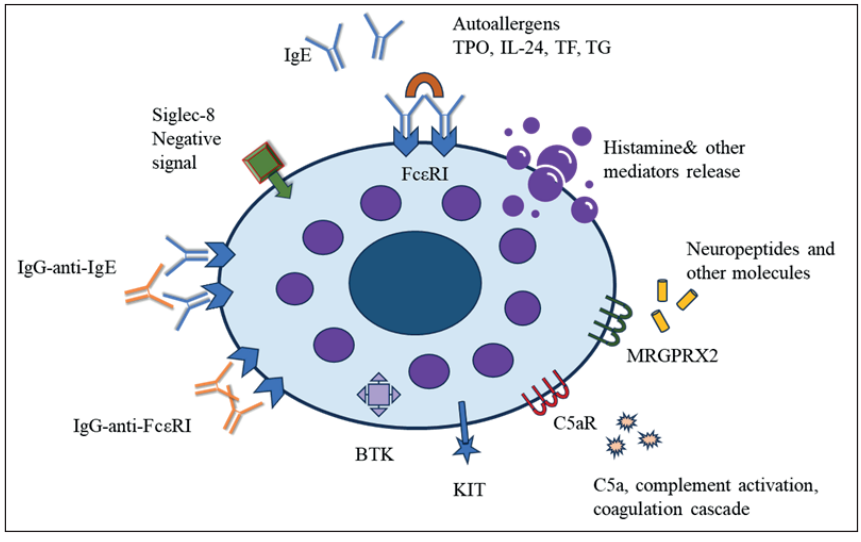

Figure 1. The figure shows the mast cell receptors and signalling pathways involved in the pathogenesis of urticaria. The main pathway for mast cell activation is FcεRI-mediated activation, but mast cells can also be activated by other receptors. All of these activation pathways are potential targets for CSU therapy.

IgE: *immunoglobulin E,* ***FcεRI:*** *high-affinity IgE receptor,* ***MRGPRX2:*** *mas-related G protein-coupled receptor X2,* ***C5aR:*** *complement 5a receptor,* ***BTK:*** *bruton tyrosin kinase,* ***TPO:*** *Thyroid peroxidase,* ***TF;*** *tissue factor,* ***TG:*** *thyroglobulin.*

(e.g., neurokinin-1 and -2 receptors [NK1Rs and NK2Rs], calcitonin gene-related peptide receptors [CGRPRs]), and neurotrophin receptors (e.g. tropomyosin-related kinase A [TrkA], TrkB and TrkC). Both MC degranulation and cytokine production are stimulated by neuropeptides such as substance P, vasoactive intestinal peptide (VIP), and somatostatin. The main receptor responsible for neuropeptide activation of MCs appears to be MRGPRX-2, although many neuropeptide receptors are expressed (6).

The mechanism that is considered to be most relevant to allergic diseases in MC activation is FcεRI-mediated activation. FcεRI is a tetrameric (αβγ2) receptor found on MCs and basophils. The α chain of FcεRI is responsible for binding IgE. IgE is found in small amounts circulating freely in the blood. It is usually found bound to its receptors on effector cells and interacts with antigen-bound IgE.

Basophils are myeloid-derived cells that develop from pluripotent progenitor cells in the bone marrow. They carry FcεRI, which is activated by IgE. Basopenia was first detected in urticaria patients approximately 60 years ago (8). In one study, different immunological phenotypes of blood basophils in patients with CSU were shown according to their response to IgE receptor stimulation: basophils reacted to FcεRI stimulation, nonreactive basophils, and nonreactive basopenic group. It has been shown that basopenic patients who do not have degranulation response to IgE receptor activation have higher disease activity (9). Additionally, basopenic patients has been characterized by autoimmune features such as increased serum autoreactivity and developed serum autoantibodies against thyroid peroxidase (TPO) (9). These findings suggest that autoimmune mechanisms may potentially play an important role in CSU patients (9).

AUTOIMMUNITY

The autoimmune theory for CSU was proposed in the 1980s, based on the higher frequency of thyroid autoantibodies and dysfunction seen in CSU patients. In 1983, it was found that the incidence of thyroid disease in CSU patients was 12%, which is twice as high as in the general population (10). Subsequently, it was observed that there was a serum factor that caused an immediate swelling response after their own serum was administered by the intradermal route in more than 50% of CSU patients (autologous serum skin test [ASST]), which strengthened the relationship between CSU and autoimmunity (11).

Currently, autoimmunity in CSU is considered as two endotypes due to different types of autoantibodies associated with MCsl activation. According to the Gell and Coombs hypersensitivity classification, CSU caused by IgE type auto-antibodies is classified as type-I endotype (type-I aiCSU), whereas CSU caused by IgG type autoantibodies is classified as type-IIb endotype (type-IIb aiCSU). Type-IIa in the Gell and Coombs hypersensitivity classification refers to the cytolytic destruction of target cells, and thus the IgG autoantibodies that cause activation are classified as type-IIb (12).

Both endotypes have similar phenotypes in terms of vasodilatation, increased extravasation, activation of sensory nerves, and collection of inflammatory cells due to MC activation. However, it is important to determine the endotype because of the differences of autoantibodies that are reflected in the clinic.

Type-I Autoimmune CSU (Autoallergic CSU)

IgE type auto-antibodies are called autoallergens. In 1999, IgE-type antibodies against TPO (IgE-anti-TPO) were detected in patients with chronic urticaria (13). Afterwards, in the study of Altrichter et al., it was found that 54% of patients with CSU had IgE-anti-TPO positivity, and there was a high rate of accompanying IgG-anti-TPO (14).

In a study comparing patients with CSU, those with autoimmune thyroiditis, and healthy controls, it was observed that IgE-anti-TPO levels were more frequently positive in patients with CSU (15). In a review conducted by Kolkhir et al., it was reported that in several studies, although not all, the prevalence of IgE-anti-TPO was significantly higher in patients with CSU compared to those with autoimmune thyroid disease and/or healthy controls (16).

Recently, Sanchez et al. demonstrated the presence of IgE-type auto-antibodies against eosinophil peroxidase (EP) and eosinophilic cationic proteins (ECP) (17). In addition, IgE type autoantibodies against double-stranded DNA (dsDNA), interleukin-24 (IL-24), tissue factor, FcεRI, thyroglobulin have been shown (18-20). Patients with CSU have IgE against more than 200 autoantigens, which is more common and different from that seen in healthy controls (19). However, further studies are needed on the pathogenic properties of these autoantibodies, as some authors have reported the presence of IgE autoantibodies such as IgE-anti-IL-24 in healthy controls (21).

Clinical Features

Considering the clinical and laboratory features of type-I aiCSU, total IgE levels are higher in patients with IgE-anti-TPO positive CSU and are accompanied by a higher rate of allergic comorbidity. In a machine learning algorithms classification study conducted by Türk et al., patients with CSU were grouped into 4 groups according to their characteristics, and it was observed that patients with high total IgE levels were accompanied by a high rate of atopic dermatitis, low ANA positivity and low IgG-anti-TPO positivity (22). In another study, high anti-IL-24 IgE levels were observed to be correlated with increased disease activity and basopenia (19). The X-CUITISE study demonstrated rapid and complete response to omalizumab, an IgE monoclonal antibody, in patients with CSU who were IgE-anti-TPO positive, and this study proved the presence of an autoallergic endotype (23).

Diagnosis

Although it is an appropriate approach to demonstrate the presence of IgE-type auto-antibodies in the serum for the diagnosis of Type-I aiCSU, it is not used in routine practice due to the difficulty of studying in many centers and lack of standardized tests. Since IgG-anti-TPO is positive in patients with IgE-anti-TPO positive CSU, it is recommended to measure IgG-anti-TPO and total IgE levels in daily practice.

Type-IIb Autoimmune CSU

IgG and IgM antibodies against IgE in patients with chronic urticaria, cold urticaria and urticarial vasculitis were first described by Gruber et al (24). In a later study, the serum of patients with CSU who had a positive ASST caused histamine release from the leukocytes of healthy donors in vitro, and an IgG type antibody against the IgE receptor was detected in these sera (25). Histamine secretion from MCs and basophils can be induced by IgG autoantibodies to FcεRI (IgG-anti-FcεRI) and by IgG antibodies to IgE (IgG-anti-IgE). Although it has been suggested that IgG-type autoantibodies may play a role in the pathogenesis of CSU and may be a subtype of CSU, the type-IIb CSU has not been clearly defined for a long time due to the inability to routinely apply tests showing IgG-anti-FcεRI and IgG-anti-IgE antibodies and their detection in healthy volunteers (26).

Recently, in the international multicenter study (PURIST) conducted to create an urticaria profile for identifying urticaria subtypes, the characteristics defining type-IIb were investigated. Autologous serum test, basophil activation test, and measurement of IgG-anti-FcεRI/IgG-anti-IgE antibodies using the ELISA method were attempted to determine the diagnostic criteria. This study showed that less than 10% of CSU patients have type-IIb aiCSU (27).

Clinical Features

Although Type-IIb aiCSU and Type I-aiCSU have a similar phenotype, they exhibit different clinical features. Type-IIb aiCSU patients have higher disease activity and longer symptom duration. Female patients are more affected, total IgE levels are lower, and the presence of autoimmune conditions such as IgG-anti-TPO positivity and vitiligo are reported to be more frequent in this group (27-29). In terms of treatment results, slower response or unresponsiveness to omalizumab and antihistamine treatments is seen (30,31). Several additional markers of type-IIb aiCSU have been identified in different studies, including low total IgA levels, nocturnal symptoms, basopenia, and eosinopenia (28,32,33).

Diagnosis

Since 2013, the diagnosis of type-IIb aiCSU has been made with the positivity of one or both of the basophil tests (basophil activation test (BAT) or basophil histamine release assay (BHRA) and serum IgG-anti-FcεRI and IgG-anti-IgE tests in addition to the positive autologous serum test (34).

ASST is an in vivo test to evaluate auto-reactivity. Auto-reactivity is characterized by the development of pruritic erythema in response to factors present in the serum after intradermal application of autologous serum. Venous blood is centrifuged and after performing positive control with histamine and negative control with physiological saline, the obtained serum (approximately 50 μl) is applied intradermally. The intradermal test is read after thirty minutes. A positive result does not define autoimmune urticaria, but may be indicative of auto-antibodies that activate MCs (35). - BHRA is based on the measurement of histamine released from allergen-stimulated basophils using a fluorometric method. BAT is the measurement of basophil activation using flow cytometry before and after allergen stimulation. Basophil activation can be detected through upregulation of selected surface

proteins, with CD63 being the most commonly used activation marker (36). CD63 is present on the membrane of secretory lysosomes of basophils and MCs, and is exposed on the surface upon degranulation. CD63 expression on the basophil surface correlates directly and strongly with histamine released into the cell supernatant (36,37).

It is recommended to confirm the diagnosis of ASST positivity with a BAT/BHRA. While only 22% of CSU patients with positive ASST were found to have positive BHRA, all patients with positive BHRA were found to be positive for ASST (26). In the PURIST study, it was observed that almost all (91%) of the BAT/BHRA-positive patients were also positive for ASST, while only 39% of the ASST-positive patients had positive basophil tests. In the same study, BAT and BHRA were shown to be 69% and 88% predictive for type-IIb aiCSU, respectively. Although ASST was initially considered to be a good, inexpensive, and widely available marker for type-IIb aiCSU, according to this study it predicts only 27% of type-IIb aiCSU cases (27).This suggests that in some patients, the auto-reactivity demonstrated by a positive ASST may be associated with clotting factors or MRGPRX2 agonist in addition to autoantibodies that cause histamine release. Recently, it has been shown that activated clotting factors do not directly activate human skin MCs and basophils, but rather cause the degranulation of these cells through complement C5a production that acts on the C5a receptor (C5aR) (38).

Antibodies that activate FcεRI can be of the IgM and IgA types as well. In a study by Altrichter et al., anti-FcεRI IgG, IgM, and IgA were detected in 24%, 60%, and 57% of patients diagnosed with CSU, respectively. In the same study, it was observed that in CSU patients who were positive for ASST, IgM-type antibodies against FcεRIa, rather than IgG-anti-FcεRI or IgE-anti-FcεRI, were more commonly associated, and high levels of anti-FcεRI-IgM were found to be associated with basopenia and eosinopenia. (39). This may be an explanation for the low predictive value of ASST observed in the PURIST study, which measured IgG autoantibodies but not IgM autoantibodies (16).

ASST positivity can also be observed in healthy individuals and in patients with other allergic or non-allergic diseases (40). Other disadvantages are that antihistamine treatment affects ASST results and false positives in the presence of dermographism.

In combination with other clinical and laboratory markers, ASST appears to be a good screening test for type-IIb aiCSU (16). For example, when ASST positivity is used together with angioedema, elevated thyroid autoantibody levels, and low total IgE levels, the likelihood of a positive BAT or BHRA result is observed to be 86.4%, 90.0%, and 100%, respectively (28). This may be useful for selecting patients for basophil testing in daily clinical practice. Although autoimmune thyroiditis is common in patients with CSU, the detection of IgG-anti-TPO alone is not specific enough to diagnose type-IIb aiCSU. Nonetheless, the combination of high levels of IgG anti-TPO and low levels of total IgE is a useful diagnostic marker for type-IIb aiCSU in clinical practice (16). It has been shown that this combination is associated with positive ASST, positive BAT results, and other type-IIb aiCSU markers (16,28,29).

The international EAACI/GA2LEN/EuroGuiDerm/APAAACI urticaria guideline recommends the evaluation of CSU patients in terms of total IgE and IgG-anti-TPO in its latest revision and update.

Coexistence of Type I and Type IIb Autoimmune Urticaria

The presence of IgE or IgG/IgM/IgA autoantibodies against self-antigens in CSU patients is not necessarily associated with type I or type IIb autoimmune endotypes. Since the expression of IgE and other autoantibody types together has not been evaluated in studies of type-IIb and type I CSU patients, the true overlap rates are still unknown. In a study by Asero et al., the co-occurrence of IgE and IgG autoantibodies against FcεRI, FcεRII, tissue factor, and thyroglobulin was evaluated in CSU patients, and IgE and IgG against one or more of these autoantigens were detected in more than 50% of patients. (41). In several studies, it has been shown that IgE-anti-TPO and IgG-anti-TPO are co-expressed in patients with CSU (14,42). In this context, it is clear that further research is needed.

CSU ENDOTYPES and TREATMENT OPTIONS

The EAACI/GA2 LEN/EuroGuiDerm/APAAACI recommends a stepwise treatment approach targeting MCs themselves or their mediators in CU. The first step of standard treatment includes second-generation H1-antihistamines, and if there is no response or partial response, the dose of the same antihistamine can be increased up to four times. Omalizumab, a humanised IgG-type anti-IgE antibody, is a recommended treatment option for antihistamine-resistant cases (1,16,43).

In a recent meta-analysis, it was observed that only 38.6% of patients responded to standard dose antihistamine therapy (44). Studies have suggested that type-IIb aiCSU is more resistant to antihistamines. Various clinical and laboratory markers, including high disease activity, positive BHRA and/or BAT results, eosinopenia, basopenia, low total IgE, and high IgG-anti TPO levels, are associated with poor response to second-generation antihistamines in type-IIb aiCSU (16). Specifically, it has been found that only 30% of patients with both high IgG-anti-TPO and low total IgE levels respond to antihistamines. Low blood basophil counts have been associated with unresponsiveness to antihistamines and positive ASST results (28,33). In a study conducted by Turk et al. in 475 patients with CSU, it was observed that patients with UAS <3 were more likely to have complete response to standard dose antihistamine, whereas higher than standard dose antihistamine treatment is needed in patients with UAS <4. Low CSU disease activity is considered to be the most important predictor of complete response to antihistamine treatment for all age groups, both by machine learning models and traditional statistics (45).

Omalizumab blocks the interaction of IgE with the high-affinity receptor FcεRI, preventing activation of MCs and basophils, as well as the binding of IgE to the low-affinity receptor (CD23) on B lymphocytes and antigen-presenting cells. Omalizumab is also able to dissociate prebound IgE from MCs and basophils, leading to reduction in mediator release by MCs (46). In a study conducted by Maurer et al, 70% of patients with CU with IgE autoantibodies against TPO who were refractory to conventional treatment responded completely to omalizumab (47).

Poor response and/or non-response to omalizumab have been associated with all type-IIb aiCSU markers including positive BHRA/BAT, low total IgE levels, high IgG-anti-TPO, as well as their combination, along with eosinopenia and basopenia (48). In the study conducted by Chen et al., it was reported that IgG-anti-TPO, an aiCSU marker, was significantly higher in non-responders compared to responders to omalizumab, and total IgE levels were lower with a high IgG-anti-TPO/tIgE ratio (49). Delayed response may be explained by FcεRI receptor down-regulation in skin MCs, which is a slow and continuous process. Patients who have delayed response to omalizumab are associated with a higher incidence of positive BHRA. In a retrospective analysis by Gericke et al., patients who were BHRA positive responded to omalizumab with a median of 29 days, while the median response time for BHRA negative patients was only 2 days. (50). Omalizumab should be initiated with the standard dose of 300 mg every 4 weeks. If the disease cannot be completely controlled with the standard dose, it should be increased up to 600 mg every 2 weeks (51).

Some patients require cyclosporine-A for CSU treatment despite the high efficacy of omalizumab in most cases. Cyclosporine-A, is an immunosuppressive agent inhibiting the activity of calcineurin, an enzyme that dephosphorylates the nuclear factor of activated T cells (NFAT). This prevents NFAT translocating to the nucleus, reducing the production of inflammatory cytokines such as IL-2, IL-3, IL-4, and TNF-a. IL-4 is particularly involved in the generation of IgE, which can induce and enhance MCs activation. Cyclosporine-A shows overall response rates of 54%, 66%, and 73% at low to moderate doses at weeks 4, 8, and 12 in CSU treatment (52). In CSU, low total IgE levels and positive basophil test results are considered as the important predictors of high response to cyclosporine treatment (53). This suggests that type-IIb aiCSU may respond better to cyclosporine according to the autoimmune subtype. The normalisation of the results of the ASST and basophil tests after treatment with cyclosporine supports this idea (54). The inhibition of histamine release from MCs and basophils explains the effect of cyclosporine. In addition, cyclosporine inhibits the proliferation of T and B lymphocytes, resulting in a decrease in the production of IgG autoantibodies that activate MCs in type-IIb aiCSU. In contrast to omalizumab, cyclosporine therapy in patients with type IIb-aiCSU may be associated with longer remission after drug reduction/discontinuation (16).

The search for new treatments that will be effective for both subtypes of CSU continues. Ligelizumab, a humanized IgG anti-IgE with 40 to 50 times greater affinity for IgE than omalizumab, was considered a promising treatment option, but its superiority to omalizumab was not demonstrated in the phase 3 study (55). Fenebrutinib, which inhibits the bruton kinase pathway that regulates FcεRI signalling in MCs and basophils, has been shown to reduce disease activity in patients with antihistamine-refractory CSU (56). Feneburitinib appears promising as a fast-acting and safe alternative in CSU. It is thought that treatments targeting the TH2 pathway may also be effective in CSU, given that CSU and atopic diseases share many common features (the key pathogenic role of MCs and IgE). Biological agents that are successfully used to treat atopic der-

Table II: New treatments under development and mechanisms of action.

Drug	Mechanism of Action	Clinical trial status
Remibrutinib	BTK inhibitors	Phase-3 (NCT05030311, NCT05032157, NCT05048342, NCT05513001)
Rilzabrutinib	BTK inhibitors	Phase-2 (NCT05513001)
Lirentelimab	Monoclonal antibody directed against Siglec-8	Phase-2 (NCT05528861)
Dupilumab	Monoclonal antibody to specifically target the IL-4 receptor alpha to inhibit IL-4 and IL-13 signaling.	Phase-3 (NCT04180488)
Mepolizumab	Monoclonal anti-IL-5 antibody	Phase-1 (NCT03494881)
Benralizumab	Monoclonal antibody specifically binds to the alpha chain of the interleukin 5 receptor (IL-5R)	Phase -2 (NCT04612725)
Tezepelumab	Monoclonal thymic stromal lymphopoietin (TSLP)-blocking antibody	Phase-2 (NCT04833855)
Barzolvolimab	Anti-KIT monoclonal antibody	Phase-2 (NCT05368285)

BTK: Bruton tyrosin kinase

matitis and asthma are also being tested in CSU. Another intracellular signalling pathway, the KIT signalling pathway, controls the differentiation, survival and activity of MCs. Barzolvolimab is a human monoclonal antibody with high specificity for binding to KIT and potentially inhibiting its function. Significant improvements in disease control and quality of life have been observed with barzolvolimab, which has been well tolerated in patients with chronic inducible urticaria. Skin MCs and circulating tryptase were rapidly and sustainably reduced (57). Some of the drugs under investigation for the treatment of CSU are listed in Table II.

In conclusion, it is important to determine the endotype of CSU for follow-up and prognosis. BAT, BHRA and specific antibody measurements of type-IIb ai-CSU markers cannot be easily applied in routine practice. There is a need to generalise these tests. Based on our current knowledge, earlier initiation of second- and third-line therapies can be considered in patients with strong type-IIb ai-CSU markers. On the other hand, the identification of biomarkers that may indicate the possibility of resistance to therapies and their routine use will help in treatment planning.

Regarding the endotypes of CSU, several points need to be clarified. The frequency or coexistence of type-I and type-II endotypes is still unclear. Further research is required to identify differences in the pathogenesis of both endotypes and their clinical implications. Extensive research is needed to develop easily accessible, specific markers or scoring systems to identify endotypes. Understanding the pathophysiology will provide the basis for the development of new therapies.

Conflict of Interest

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