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REVIEW

Immunopathogenesis of urticaria: a clinical perspective on histamine and cytokine involvement

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Abstract

Background Urticaria is a clinical condition characterized by the appearance of wheals (hives), angioedema, or both. Over the last several decades, a better understanding of the mechanisms at play in the immunopathogenesis of urticaria has underscored the existence of numerous urticaria subtypes. Separating the different kinds of urticaria explicitly helps find the best detection method for the management of this skin disorder. Subtypes of urticaria also include both spontaneous and physical types. The conventional ones include spontaneous urticaria, constituting both acute and chronic urticaria. Therefore, a broad and effective therapy is essential for the diagnosis and treatment of urticaria.

Methods To understand the immunopathogenesis of urticaria, various databases, including PubMed, Scopus, and Web of Science, were used to retrieve original articles and reviews related to urticaria. While information on several clinical trials were obtained from clinicaltrials.gov database.

Results This article highlights the immunopathogenesis involved in the intricate interaction between cellular infiltration, immune reactions, coagulation cascades, and autoantibodies that underlie urticaria's pathophysiology.

Conclusion The recent progress in understanding urticaria can help to understand the intricate characteristics in the immunopathogenesis of urticaria and could play a beneficial role in the management of urticaria.

Keywords Urticaria · Diagnosis · Subtypes · Cytokines · Mast cell · Histamine

Abbreviations

AAS	Angioedema Activity Score
ADGRE2	Adhesion g-protein-coupled receptor e2
AECT	Angioedema control test
AE-QoL	Angioedema- quality of life questionnaire
ASST	Autologous serum skin test
AU	Acute urticaria
BCR	B cell receptor
BTK	Bruton's tyrosine kinase
C5aR	Complement component 5 receptor
CholU-QoL	Cholinergic urticaria-quality of life questionnaire
CholU	Cholinergic urticaria

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CholUAS	Cholinergic urticaria activity score
CHRM3	Cholinergic receptor m3
CIndU	Chronic inducible urticaria
ColdU	Cold urticaria
ColdUAS	Cold urticaria activity score
COX1	Cyclooxygenase 1
CRP	C-reactive protein
CRTh2	Chemoattractant receptor- homologous molecule expressed on t helper 2 cell
CSU	Chronic spontaneous urticaria
CU	Chronic urticaria
CU-Q2oL	Chronic urticaria-quality of life questionnaire
dsDNA	Double-stranded deoxyribonucleic acid
ECP	Eosinophil cationic protein
EPO	Erythropoietin
ESR	Erythrocyte sedimentation rate
FP	Fusion protein
HIV	Human immunodeficiency viruses
ICAM	Intercellular adhesion molecule
IL-6	Interleukin-6
ILC-2	Skin-resident group 2 innate lymphoid cells
IV	Intravenous
LPS	Lipopolysaccharides
LYN	Lck/yes novel tyrosine kinase
mAb	Monoclonal antibody
MBP	Myelin basic protein
MCP3	Monocyte chemotactic protein-3
MRGPRX2	Mas-related g protein coupled receptor × 2
NSAID	Non-steroidal anti-inflammatory drugs
OSMRβ	Oncostatin M receptor- β
PAF	Platelet activating factor
PAR1	Protease-activated receptor-1
PAR2	Protease-activated receptor-2
PAR3	Protease-activated receptor-3
PECAM	Platelet endothelial cell adhesion molecule
RANTES	Regulated upon activation normal T cell expressed and secreted
SC	Subcutaneous injection
SCF	Stem cell factor
Siglec 8	Sialic acid- binding immunoglobulin- like lectin 8
SM	Small-molecule drug
SYK	Spleen tyrosine kinase
TGF	Transforming growth factor
TNF	Tumour necrosis factor
TPO	Thrombopoietin
TSLP	Thymic stromal lymphopoietin
UAS	Urticaria activity score
UAS	Urticaria activity score
UCT	Urticaria control test
UTI	Urinary tract infections
VCAM	Vascular cell adhesion protein
VEGF	Vascular endothelial growth factor

Introduction

Urticaria encompasses a collection of disorders characterized by a distinctive pattern of cutaneous reactions. It is estimated that approximately 20% of individuals worldwide will experience urticaria at some point during their lifespan [1, 2]. Urticaria occurs when mast cells in the skin become hyperactive and degranulate, releasing several mediators along with histamine that stimulates sensory nerves, cause vasodilation and eventually, plasma leaks out of the blood vessels and recruits more cells [3, 4]. The emergence of the classic symptoms of this disorder include itchy wheals (hives) and angioedema. Compared to its more transient counterpart, acute urticaria (AU), chronic urticaria (CU) typically persists for a duration exceeding six weeks [4]. There are two other categories of CU: inducible and spontaneous. In inducible urticaria, an external stimulus, such as cold in cold urticaria (ColdU), triggers an urticarial reaction. It is unclear what causes spontaneous urticaria; however, stress, infections, and other aggravating factors may precipitate symptoms in certain people. A single patient can simultaneously experience spontaneous and induced urticaria [4–6].

Though most cases of AU clear up after a week, a significant percentage (40%) persists for a longer duration. In many cases, CU continues for years before going into spontaneous remission. However, some patients may have a connection to diseases or certain drugs or foods. Most cases of AU arise spontaneously and without apparent reason. Chronic spontaneous urticarial (CSU), also known as chronic idiopathic urticaria, seems to have two known causes: involvement of autoantibodies; IgE (type I or autoallergy) and IgG (type IIb or autoimmunity). There is currently no very well-known explanation for what causes chronic inducible urticaria (CIndU) [7, 8]. Autoantibodies that activate mast cells, promote cell infiltration, agglomeration, and activate complementary systems that play essential roles in CSU pathogenesis [9, 10]. Patients and society at large bear a disproportionate share of the cost of CU. There is substantial evidence that CU symptoms negatively impact health-associated living standards [11, 12]. These symptoms include trouble sleeping, decreased physical and mental well-being, and subpar academic and occupational performance. About a third of those with CU are not helped by the current therapeutic choices. Several potential medications are already in the developmental stage, but new targeted treatments are urgently needed.

This study aims to examine the present state of knowledge on the immunopathogenesis of urticaria and its diagnosis

and treatment. Additionally, this article also aims to serve as a comprehensive resource for clinicians and researchers, particularly dermatologists, in the effective management of urticarial conditions, with the ultimate goal of enhancing the quality of life for affected patients.

Rate of occurrences

In 2017, it was projected that there were 160 million new cases of urticaria worldwide, making the prevalence estimate for the year 86 million. However, the frequency of each form of urticaria varies throughout populations. CU, particularly CSU, has a higher occurrence and incidence among women aged 30 years and older, while the highest AU prevalence is observed in children under the age of 5 [6, 13–21]. Generally, patients suffering from CSU were found to be older in age than CIndU patients with an average age range of 30–70 years for the former and 20–40 years for the latter. CSU typically manifests between the ages of 30 and 50 years, while CIndU occurs in patients of 20–35 years of age. Both men and children are more likely to get cholinergic urticaria (CholU), but all other types of urticaria have a female predominance in adults [21].

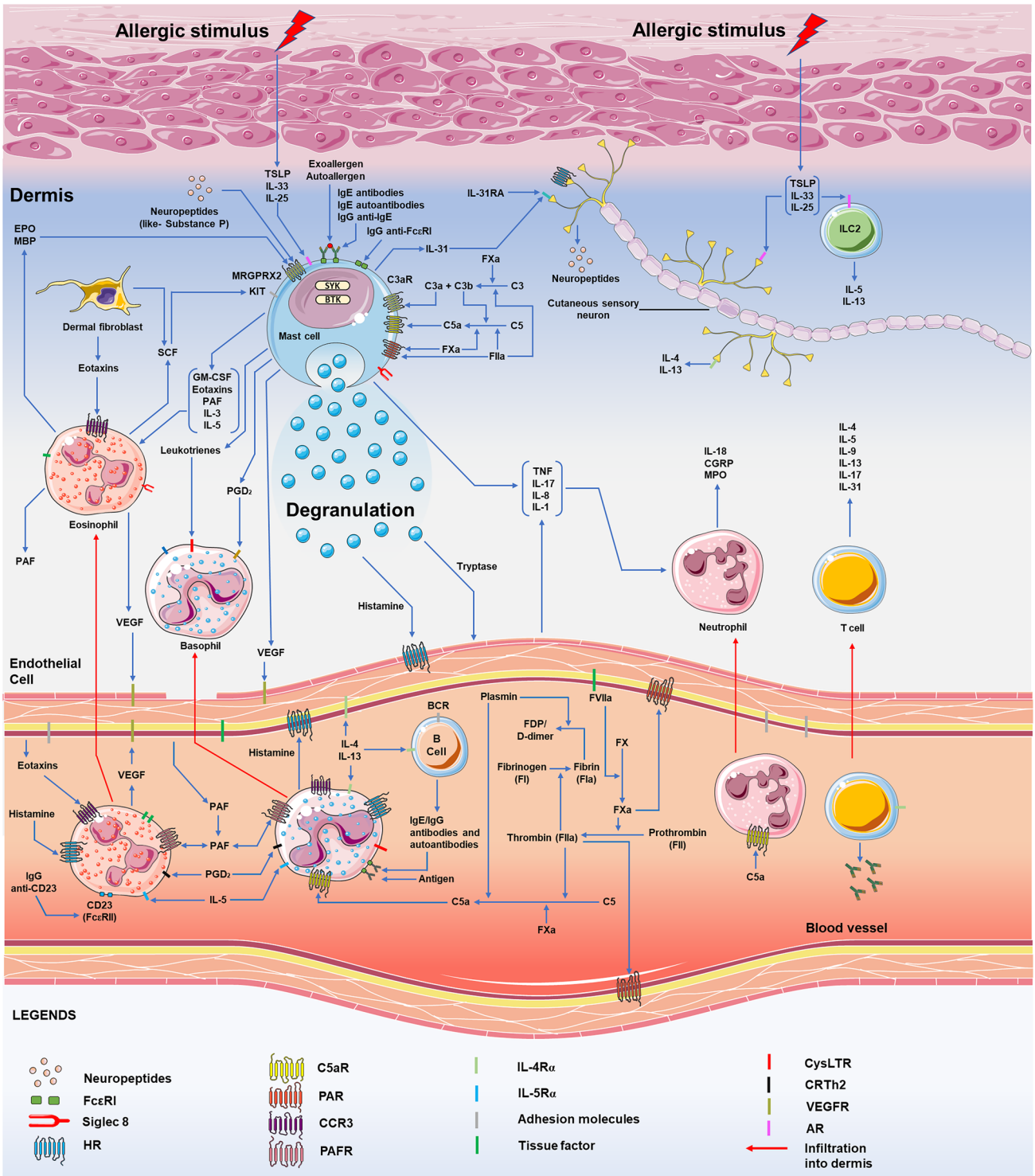
While both AU and CU can affect individuals from diverse racial backgrounds, several studies [15, 19, 22, 23] have reported a higher prevalence of these conditions among patients of colour. In general, AU has a lifetime prevalence ranging from 6 to 19%, while other forms of urticaria have a prevalence ranging from 3 to 22%. The overall lifetime incidence is approximately 4.4%. Point prevalence, which typically considers prevalence after one year, is around 1.5% in the United States and Europe, and between 3 and 4% in Korea, China, and Mexico [22]. It is possible that distinctive demographic, environmental, and behavioural trends in places like Italy, Taiwan and South Korea [21, 24–27], among others, contribute to the rising CU rates. Compared to CSU [6, 28] CIndU is much rarer. Across all CU cases, the combined incidence of all CIndU subtypes was 13% [29] whereas the incidence of CSU was between 60 and 90%. From the symptomatic dermographism, it was found that CholU and ColdU are the most prevalent types of CIndU in both adults as well as children. Heat urticaria, sun urticaria, aquagenic urticaria, contact urticaria, and vibratory angioedema collectively represent only 2% to 3% of all CU cases [21, 30]. Up to 36% of CU patients also experience delayed pressure urticaria, but this condition typically occurs concurrently with CSU. The median duration of an AU episode is around one week. Progression from AU to CU varies among studies, with estimates ranging from approximately 5% to 39%. CSU has a shorter mean or median disease duration than CIndU, and the cumulative weighted average estimates remission on their own 17% after 1 year, 45% after 5 years, and 73% after 20 years [31]. Recurrence of symptoms is reported in only 3% to 31% of individuals with CSU.

The average or median duration of CIndU was 2–12 years, while its three most common subtypes symptomatic dermographism lasted 2–5 years, CholU lasted 3–8 years, and ColdU lasted 2–9 years. Within 5 years, one-third of CIndU patients experience remission. The remission percentage is highest in the case of symptomatic dermographism. Both CholU and ColdU have the lowest remission percentage. Phenotypic, endotype, clinical, laboratory aspects and therapy response in urticaria have all been linked to different causes and indicators of the disorder [31].

Factors associated with urticaria

High population density [15], an individual's or family history of allergy disease [32], or both, [33] have all been cited as possible contributors to the development of AU. Some scientific investigators have found a correlation between high income and low risk for CU, whereas others have found a correlation between high risk for AU with poverty or low socioeconomic status [34, 35]. In a twin study, genetic variables may contribute to urticaria susceptibility. Several polymorphic genes, including *TNFRS11A*, *TBXA2R*, and *PLA2G4A*, have been linked to susceptibility to NSAID-induced AU and/or angioedema [36, 37].

There is evidence that genes showing polymorphism and encoding interferon-gamma, interleukin-6, interleukin-17 receptor antagonist, interleukin-10, transforming growth factor beta, tumour necrosis factor (TNF), interleukin-2, interleukin-1, HLA class I and II alleles and PTPN22 contribute susceptibility to chronic uveitis. Susceptibility to autoimmune disorders can also be attributed to specific genes like HLA alleles and PTPN22 [38]. Examples of additional autoimmune disorders are type 1 diabetes mellitus, rheumatoid arthritis and HLA- DR4 that have been linked to autoimmune CSU, as characterized by a positive release of histamine from basophils [39]. The risk of having an autoimmune disorder within 10 years of a CSU diagnosis is significantly greater, especially in women of middle age with autoimmune CSU [40]. Compared to the control group, CSU patients' odds of hypothyroidism or rheumatoid arthritis were 23 and 20 times higher, respectively. Systemic lupus erythematosus, celiac diseases, rheumatoid arthritis and type I diabetes mellitus [41] were diagnosed before CSU in 80% of patients and after CSU in 20%. Autoimmune thyroid disease patients, especially women, had a much greater risk of developing CSUs [42]. The prevalence of a family history of CSU was highest among individuals with positive indicators of autoimmune urticarial [43–46], affecting up to 25% of



patients with CSU. Additionally, women who suffer from peptic ulcer disease or irregular uterine bleeding are more likely to develop CU [47, 48]. According to reports, CholU and ColdU occur at different rates in different parts of the world, indicating that environmental factors like altitude and temperature may increase susceptibility to CIndU [49].

◂**Fig. 1** The immuno-pathogenesis of urticaria and its development is based on the sequential activation and degranulation of histamine and other involved mediators, leading to various activities such as dilation of dermal blood vessels, sensory nerve activation (itch) and induction of plasma extravasation (oedema and cellular infiltration). In allergic urticaria, liberation of alarmins which includes IL-25, IL-33, and TSLP, lead to the activation of epithelial cytokines and result in the activation of ILC-2 and the differentiation of T cells into T helper 2 (TH2) cells that subsequently secrete TH2 cytokines. Activated allergen specific TH2 cells are primarily responsible for producing IL-13, IL-4 and IL-5. After that, B cells cause allergens to form a cross-linking with IgE–FcεRI complexes on the mast cells' surface, resulting in its activation. Complex interlinked multistep molecular events characterize CSU. These events encompass cellular infiltration (eosinophils, basophils and T cells are primarily involved), IgE/IgG mediated release of histamine, Itch signalling molecular mechanisms regulated by cutaneous pruriceptive sensory nerves, which include both histamine-dependent and independent pathways collectively contributing to inflammation of sensory neurons, complementary cascade activation such as through anaphylatoxin C5a production and tissue factor-initiated extrinsic pathway belonging to the coagulation cascade. It is pertinent to mention the different receptors such as FcεRI, signalling pathways (such as SYK and BTK) and mediators (such as histamine) responsible for the activation of the mast cells, eosinophils, immune cells, and /or different immune cells that are involved in the pathogenesis of urticarial. These are potential therapeutic targets presently being targeted for currently available therapies or developing a novel therapeutic agent. Similarly, autoallergy and/or autoimmunity have been implicated in the development of CIndU

Treatment and annual healthcare expenditures

Significant healthcare consumption and economic hardship are linked with urticaria, especially CU. This includes both planned and unplanned doctor's visits, laboratory spending fees, and lost productivity and income as a result of missed work [11, 50]. Compared to the general population, those with CU and related conditions such as angioedema were more likely to seek medical attention, including more visits to primary care physicians, specialists in allergy and dermatology, and hospitals [12, 49, 51]. In children (15.5% vs. 9.9%) and adults (7.8% vs. 4.6%), individuals with CIndU were more likely to require hospitalization than those with CSU.

Immunopathogenesis of urticaria

The skin's numerous mast cells are critical in urticaria's aetiology. Besides the superficial and deep dermis, the subcutis also contains these cell types, and are concentrated around the sensory nerves and cutaneous blood vessels. Itchy wheals and/or angioedema result from their activation and subsequent degranulation [3], which causes acute urticaria. ASU, wheals, and/or angioedema have been associated with type I hypersensitivity reactions produced in response to food, medications, and other types of allergens in patients with anaphylaxis [52].

By attaching to a preformed complex of an IgE antibody attached to its high-affinity receptor, FcεRI, exoallergen activates and degranulates mast cells and basophils [53]; this is known as type I hypersensitivity or an instantaneous IgE-mediated reaction. Pharmacological inhibition of cyclooxygenase 1 (COX1) and elevated levels of cysteinyl leukotrienes are common causes of NSAID-induced urticaria and/or angioedema [54]. Direct contact with allergens after sensitization [55] or urticariogenic compounds such as stinging nettles [4] can cause acute contact urticaria in unsensitized individuals.

Current and future therapies for CSU aim to specifically target the activation of mast cells, including their signals, receptors, signalling pathways, inhibitory receptors, and mediators. These components are crucial in developing wheals and angioedema associated with CSU [3, 10, 13]. Different signals activate the many activation receptors found in mast cells [13]. Examples include MRGPRX2, FcεRI, PAR1, C5aR, PAR2, PAR3, cytokine receptors and chemoattractant receptor-homologous molecules produced on helper T cells (CRTh2). The interaction between stem cell factor (SCF) and its receptor KIT (CD117) on mast cells significantly impacts various aspects of mast cell biology, including differentiation, survival, migration, proliferation, and apoptosis. SCF is produced by multiple cell types, including fibroblasts, endothelial cells, and mast cells themselves [56]. Several cytoplasmic signalling proteins, for instance, spleen tyrosine kinase (SYK), bruton's tyrosine kinase (BTK), and LYN phosphorylate downstream signalling targets, causing mast cells to activate and degranulate must work together to activate FcεRI. [57]. Signaling through the FcεRI begins with LYN phosphorylating the β and γ chains of the receptor, which in turn activates SYK and BTK (Fig. 1). FcεRI-mediated mast cell activation and production of cytokines are positively regulated by the cytosolic tyrosine kinase BTK. It has been demonstrated the critical role of Bruton's tyrosine kinase (BTK) in the activation of the B cell receptor (BCR), which is also involved in the activation of mast cells [57, 58]. Mast cells not only produce a small number of inhibitory receptors that, once bound to their ligands, can shut down mast cells and stop them from becoming active e.g. CD200R, siglec 8, FcγRIIb and CD300a [59]. Histamine is the primary player in the onset of CSU symptoms; however, other modulators such as tryptase, prostaglandin D2 (PGD2), tumour necrosis factor (TNF), IL-5, IL-13, IL-4, IL-17, and IL-31 are also involved. These mediators influence both the skin cells that are already there and the Basophils, T cells and eosinophils which get triggered during immune reaction [3, 13] (Fig. 1).

Cellular infiltration

CSU exhibits perivascular and interstitial inflammatory cellular infiltrates comprising eosinophils, neutrophils, lymphocytes, and basophils, resembling an allergic late-phase reaction [9, 60–62]. MCP3, Eotaxins, IL-5, RANTES, IL-17, C5a, C3a, platelet-activating factor (PAF), activated endothelial cells, and TNF from mast cells, TH2 cells, dermal fibroblasts, and other sources potentially facilitate the migration of infiltrating cells from blood to skin. Histamine, TNF, thrombin, and other factors increase cell adhesion molecule expressions (E-selectin, P-selectin, VCAM, PECAM, ICAM) on endothelial cell surfaces and CSU-affected skin areas, contributing to this phenomenon (Fig. 1) [9].

Eosinopenia and basopenia in blood, found in around 10–15% of CSU patients, may indicate cellular migration into the skin. These symptoms are associated with autoimmunity, CSU activity, and suboptimal response to H1 antihistamines (H1-AH) and omalizumab [63, 64]. Within 30 min of injecting autologous serum intradermally, wheals exhibited perivascular neutrophils and eosinophils, succeeded by a rise in T lymphocytes [65]. Activated basophils that have migrated to blood and skin can release leukotrienes, histamine, and cytokines via FcεRI and C5aR activation, contributing to CSU's pathophysiology [66, 67]. CSU patients show increased eosinophil granules in wheals [68, 69] particularly involving MBP, which activates and degranulates mast cells. This suggests a potential interaction mechanism between eosinophils and mast cells [68]. Eosinophil activation can result from IgG autoantibodies targeting the low-affinity IgE receptor or mast cell mediators like TNF, IL-5, eotaxin, and PAF (Fig. 1) [70, 71]. Activated eosinophils can also release SCF, a mast cell growth factor. In summary, eosinophils play a vital role in activating the coagulation cascade, mast cells, and Mas-related G-protein-coupled receptor X2 (MRGPRX2) through tissue factor production and MRGPRX2 agonist release [68, 71].

CSU skin biopsy samples reveal not only TH2 cells but also TH1 and TH17 cells [9]. TH2 cells are common in allergic conditions due to their cytokine production, which stimulates IgE synthesis and activates basophils, mast cells, and eosinophils. CSU patients' blood and lesional skin have elevated cytokine levels and expressions. These include IFN, TNF, TGF, IL-1, IL-3, IL-4, IL-5, IL-6, IL-13, IL-17, IL-23, IL-24, IL-31, and IL-33.

Coagulation cascade and complement system

Inducers like histamine, LPS, TNF, VEGF, IL-6, IL-1, and IL-33 can exhibit substantial tissue factor expression in eosinophils and cutaneous microvascular endothelial cells [72]. Activation of coagulation factors like factor Xa (FXa) and FIIa occurs through the extrinsic coagulation pathway, triggered by tissue factor inducers [73, 74].

Tissue factor inducers and mediators activate mast cells, causing wheal and flare through vascular plasma leakage. Extravascular plasma holds autoantibodies to FcεRI and IgE-bound mast cells under the skin [9, 75]. Mast cell degranulation can result from thrombin and FXa action, impacting pseudoautosomal regions [10, 76].

Extrinsic coagulation, fibrinolysis, or IgG anti-FcεRI binding to basophils and mast cells are necessary for generating complement component C5a [10]. Active coagulation and plasmin factors create C5 derivatives (C5a & C5b) and C3 derivative (C3b). Leached plasma holds C5a and C3a, which activate basophils and mast cells through C5aR and C3aR, respectively [10, 77]. In summary, tissue factor-stimulated peripheral basophils release leukotriene C4 in the presence of functional-specific IgE antibodies to tissue factor [78]. Coagulation and fibrinolysis activation is believed to stem from CSU. Blood biomarkers like D-dimer, indicative of thrombin production and fibrinolysis, rise in severe CSU cases and decrease during remission [79]. Furthermore, a study revealed that D-dimer could be a possible marker in a subset of patients suffering from CSU [80]. Elevated D-dimer levels in severe autoimmune urticaria may not always indicate the need for anticoagulant medication. Reducing D-dimer levels can lower the proinflammatory state by successfully controlling the symptoms of the patients. Researching the substantial association between elevated D-dimer levels and type IIb autoimmune CSU, together with resistance to omalizumab, might be promising for early diagnosis. It is been further noted that in individuals suffering from severe autoimmune CSU, cyclosporine medication reduces D-dimer levels more than anticoagulant therapy does during immunosuppressive therapy [81]. In CSU patients, elevated CRP levels were positively correlated with increased C3, C4, IL-6, and D-dimer levels, Autologous Serum Skin Test (ASST) positivity, and CSU activity [79, 82]. This underscores the close connection between autoimmune, inflammation, complement, and coagulation pathways in chronic urticarial syndrome's pathogenesis, potentially contributing to the perpetuation and exacerbation of urticarial inflammation (Fig. 1).

Interplay of autoantibodies in CSU

IgE, IgA, IgM, and IgG antibodies are pivotal in CSU's pathophysiology [83–85]. Adequate IgE concentrations bind to FcεRI's α subunit, activating basophils and mast cells, regardless of the antigen [86]. In allergic, autoallergic, and autoimmune urticaria, IgE cross-linking by allergens, autoallergens, and IgG anti-IgE antibodies can trigger mast cell and basophil activation, resulting in mediator release [8, 85, 87, 88].

Many CSU patients exhibit IgE antibodies targeting autoantigens like TPO, EPO, tissue factor, dsDNA, ECP, FcεRI, IL-24, and thyroglobulin. In vitro research suggests that specific antibodies, such as anti-IL-24, IgE, and IgE anti-TPO, can activate mast cells and/or basophils [8, 89, 90]. Effective passive transmission of IgE anti-thyroid peroxidase (TPO) has been observed. CSU patients with elevated IgE anti-TPO levels show high positive TPO skin prick test rates, providing further evidence of IgE antibodies' role in CSU's origin [91]. Autoallergens like IL-24 are produced in the skin. Cross-reactivity between proteins such as TPO (absent in the skin) and EPO (present in the skin) could clarify why IgE and autoallergens activate mast cells only in the skin and not other organs [92, 93]. Recent studies indicate that around 20% to 50% of CSU patients possess these autoantibodies [94]. Diagnosing autoimmune CSU linked with these autoantibodies necessitates ELISA-detected antibodies (IgG), confirmed skin auto-reactivity via ASST, and basophil activation testing. However, only 8% of CSU patients meet autoimmune CSU criteria [7, 95]. The clear distinction and separation of autoIgE and IgG endotypes remain debatable. It's increasingly evident that a single patient might exhibit IgG autoantibodies alongside other types like IgA, IgE, and IgM. Yet, actual overlap rates remain uncertain [84, 85]. Blood autoantibodies, especially IgE autoantibodies, may arise initially, while over time, different classes of autoantibodies can develop during the disease progression.

Inflammatory nerves in CSU

Histamine, interleukin-31 (IL-31), neuropeptides, and mediators like that have been postulated to mediate the non-monodirectional interaction between immune cells, sensory nerves and mast cells in CSU [68, 96, 97]. Mast cell activation through MRGPRX2 could perpetuate the symptom cascade in urticaria, including pruritus, vasodilation, plasma leakage, and neurogenic inflammation [98]. MRGPRX2, reacting to various chemicals, triggers mast cell activation without IgE [99]. Application of MRGPRX2 agonists worsens skin reactivity in CSU-diagnosed individuals. CSU patients have an excess of mast cells expressing the MRGPRX2 gene. Elevated levels of neuropeptide-like substance P and MRGPRX2 agonist are observed in CSU patients [100, 101].

Pathogenesis of chronic induced urticaria

Passive transfer and/or omalizumab effectiveness show that autoallergic IgE-mediated mast cell activation is evident in conditions like ColdU, symptomatic dermographism, CholU, and solar urticarial [102]. Autoantibodies of IgE type might form in reaction to skin-secreted proteins, as seen with cold-induced protein secretion [103]. Mast cell activation in solar urticaria is linked to chromophore attachment, molecularly altered by sunlight, to IgE on mast cells [104]. CholU symptoms may arise from sweat antigen generation due to blocked sweat gland ducts with serum antibodies against MGL 1304 sweat antigen detected [105]. CholU might induce acetylcholine escape, degranulating mast cells via reduced M3 receptor expression in the epithelial cells of the sudoriferous gland [105]. ColdU shows IgM and/or IgG antibodies against IgE. Heat urticaria individuals rarely react positively to intradermal testing using hot autologous serum, likely due to inactivated complement and denatured IgE in the serum [103, 106]. Gain-of-function mutations in the G-protein-coupled receptor E2 on mast cells can lead to autosomal dominant hereditary vibratory angioedema. This mutation might weaken the connection between the receptor's α and β subunits, increasing mast cells' susceptibility to vibration-triggered degranulation [107]. Histamine is one of multiple pro-inflammatory mediators in delayed pressure urticaria, along with TNF and interleukin family members. Delayed pressure urticaria, distinct from other CIndUs, shows significant dermal leukocyte infiltration due to a delayed onset stimulus [108]. Contact urticaria can result from either a non-immune reaction or an immunological response involving IgE or T cells [109]. Multiple theories have emerged to explain aquagenic urticaria's origin, including factors beyond a histamine-dependent mechanism. Enhanced passive diffusion of water and water-soluble antigens (epidermis) are also suggested contributors [110].

Prevention, screening, and diagnosis

Diagnosis

Urticaria presents consistently across age, race, and gender. Angioedema and wheals share the same distribution regardless of skin colour, although erythema from wheals can be harder to detect on darker skin [111]. Diagnosis involves

personal history and physical examination, considering patient photos or symptom documentation. Despite subtypes, urticaria is typically diagnosed accurately and swiftly.

Acute urticaria

Acute urticaria (AU) is self-limiting and often doesn't require extensive diagnostics. Immediate symptom onset after allergen contact might warrant allergy testing to prevent re-exposure in patients with hypersensitivity or food allergies caused by drugs.

Chronic spontaneous urticaria

Wheals are the predominant symptom in CSU patients (57%), followed by angioedema and wheals (37%), and simple angioedema. Circadian fluctuations in mast cell activation and underlying pathophysiology may explain the spontaneous occurrence of CSU symptoms, with a higher likelihood during evening and nighttime [112, 113]. Night-time symptoms, for instance, have been linked to the autoimmune endotype CSU [114]. Wheals are most frequently observed on the arms and legs but can appear anywhere. Angioedema commonly occurs on the lips and eyelids, though it can manifest on other body parts like the feet and hands [1]. Moderate to severe CSU typically manifests as daily, near-daily, or intermittent-recurrent wheals and/or angioedema [4]. CSU exacerbations are associated with triggers such as stress, specific foods, medications (especially NSAIDs), and infections. Over 30% of CSU patients experience NSAID hypersensitivity, verified by oral drug provocation testing that induces CSU exacerbation following COX1 inhibitor intake. Selective COX2 medications are usually better tolerated [54, 115]. Specialised treatment includes assessing total serum IgE and IgG anti-TPO levels in all CSU patients. Elevated IgG anti-TPO levels could indicate autoimmune CSU [7, 40, 116]. Recent studies suggested that thyroid autoimmunity is not useful for classifying CSU patients. Baseline total IgE levels have emerged as the most reliable prognostic indicator for predicting omalizumab response in individuals with autoimmune CSU [117, 118].

Chronic inducible urticaria

CIndU patients usually have shorter-lasting wheals (1 h) than CSU patients (up to 24 h). Frequent exposure to triggers and low sensitivity contribute to significant pathological activity [4, 109]. Systemic reactions like anaphylaxis can occur; high-risk patients should have adrenaline autoinjectors, even if lesions are mainly confined to trigger-exposed skin areas [119]. Approximately half of individuals experience improvement in their CU during pregnancy, while about a third experience worsening [120]. Pregnancy can worsen the severity of CU, particularly in cases of combined CIndU and CSU. Diagnosis of CIndU involves a thorough history and provocation testing to identify triggers and assess disease activity. Validated provocation testing tools (Fig. 2) are available for most CIndU subtypes, aiding in quantifying disease activity and tracking treatment effectiveness.

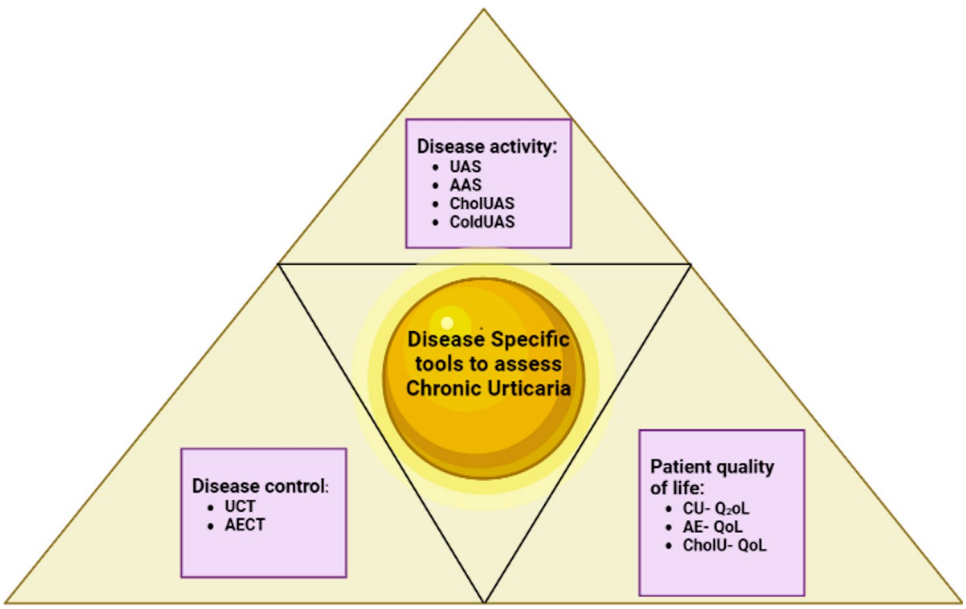


Fig. 2 Depicts tools to assess the control, activity and patient's quality of life in case of chronic urticaria

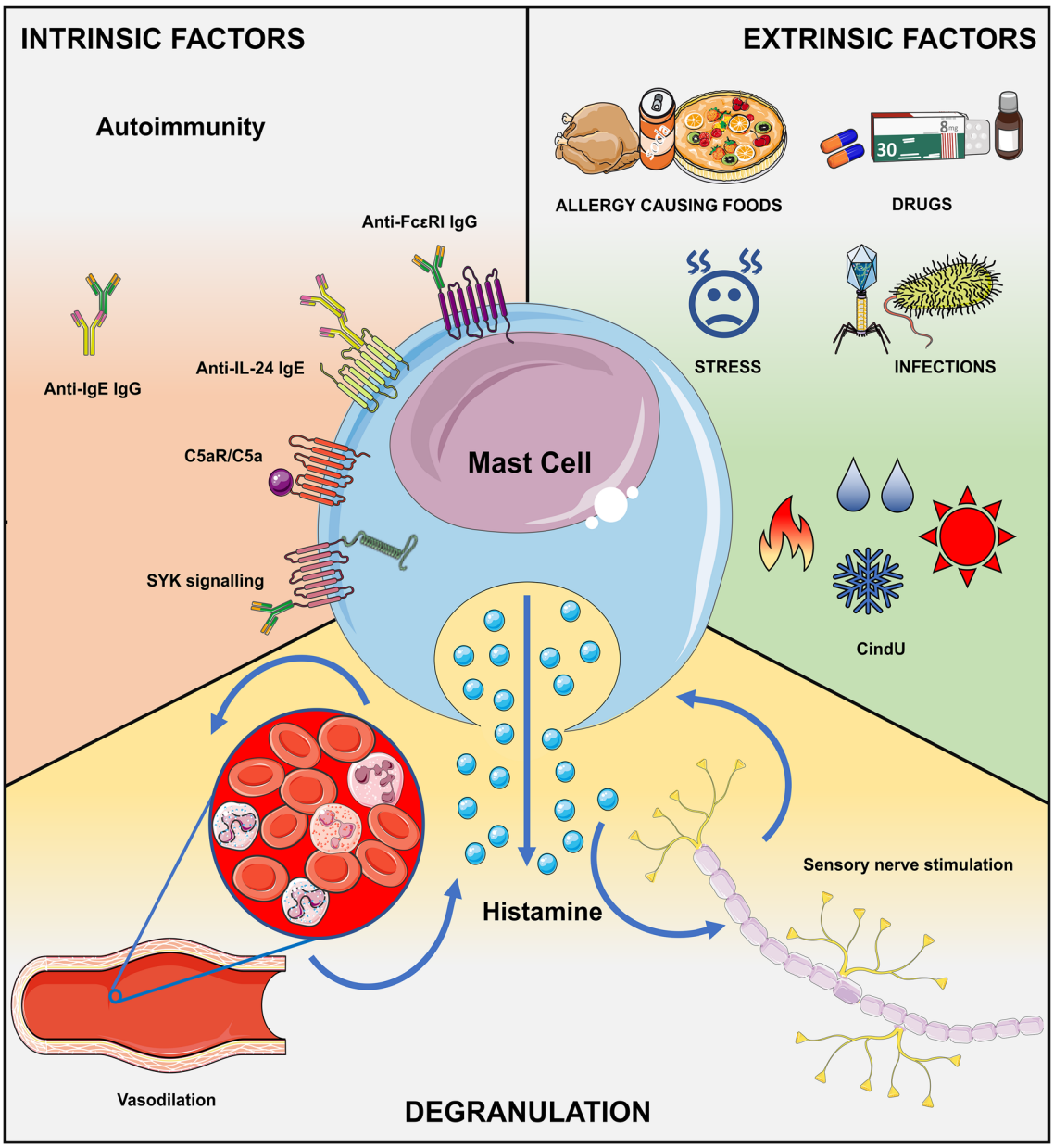


Fig. 3 Factors affecting the degranulation process leading to the release of histamine eventually causing sensory nerve stimulation and peripheral vasodilation

Comorbidities

Acute urticaria

Reactions caused by foods, stress, Hymenoptera stings, and physical factors are less frequent compared to triggers like NSAIDs and antibiotics. Infections can complicate diagnosis, as anti-inflammatory drugs used for infections can obscure the cause of urticaria. While inducible factors play a minor role in childhood AU, they contribute significantly to around 15% of adult AU cases [121]. Patients aged 0–6 years were more likely to have their AU's cause identified than those aged 7–18 years [52]. In children younger than 13, AU was primarily triggered by food and infection, whereas in adolescents aged 13–18, these factors were less commonly associated [52]. Chronic spontaneous urticaria (AU) often disappears after treating the underlying infection or stopping the triggering medication (Fig. 3).

Chronic spontaneous urticaria

Most studies reveal rates of CIndU that are more than 10%; this indicates that it is a common comorbidity of CSU. Patients diagnosed with CU showed a prevalence of CSU ranging from 29–93%, CIndU ranging from 6–35%, and 1–43% having both CSU and CIndU. 36% of the 245 individuals diagnosed with CSU had CIndU, which was determined by a positive challenge test. Most patients exhibited symptomatic dermographism (25%), followed by ColdU (13%) [48]. A patient can have more than one form of CIndU besides CSU [122].Patients suffering from CSU, likely to have an autoimmune disease than the general population (28% vs. 1–2%, respectively). Rheumatoid arthritis, autoimmune gastritis, vitiligo and diabetes mellitus are the most common autoimmune diseases seen in patients at CSU. Autoimmune thyroid diseases account for 25% of all cases, with the most common form being Hashimoto's thyroiditis, which can occur with or without hypothyroidism [40, 123]. While up to 77% of individuals with CSU5 are reported to have *Helicobacter pylori* and dental infections, the connection between bacterial infections and CSUs remains limited and contradictory [5]. Viral infections (hepatitis, HIV) and fungal infections are unlikely contributors to CSU development, with unclear clinical significance [5]. CU didn't affect the progression of COVID-19, but in a trial, about one-third of patients, particularly those with severe cases, experienced worsened CU symptoms during COVID-19 infection [124]. The link between CSU and parasitic infections remains unclear, but treating proven parasitic infections with antiparasitic medications improved CSU symptoms in about one-third of cases [5]. Increased rates of allergic conditions haven't consistently been shown in CSU patients [5].

Three extensive studies have indicated that patients with CSU are more likely to have allergic diseases than the general population or healthy groups without urticaria [34, 125, 126]. CSU patients have a history of cancer, mainly non-hematologic types, and sometimes CSU resolves after the patient enters remission [5, 26, 127]. Cancer-induced immune system dysfunction can activate complement and coagulation cascades, potentially contributing to CSU development in cancer patients. The resolution of CSUs after cancer treatment might reflect the restoration of immune homeostasis [128]. Around 60% of CSU patients face mental health challenges, primarily depression and anxiety, which considerably impact their overall quality of life [5].

Chronic inducible urticaria

The Coexistence of CIndU and CSU is possible. Among individuals with symptomatic dermographism, 71% also reported CSU, while the figures were 25% for CholU and 10% for ColdU [119, 129, 130]. CholU, solar urticaria, ColdU, and symptomatic dermographism often coexist with allergic disorders, with a prevalence ranging from 26 to 48% [131–134].

Differential diagnosis

Wheals and/or angioedema can be related or prodromic signs in patients with conditions beyond urticaria [135]. Comprehensive evaluation involving history, physical examination, and tests is necessary to diagnose or rule out other potential causes of CSU. In cases with wheals but no angioedema, it's crucial to consider excluding autoinflammatory conditions like Schnitzler syndrome and cryopyrin-associated periodic syndromes [4]. Wheals in individuals with autoinflammatory syndromes often do not respond well to antihistamines, leading to a distinct condition called neutrophilic urticarial dermatosis. This condition is characterised by concentrated perivascular and interstitial infiltration of neutrophils infiltration around blood vessels, known as leukocytoclasia, without vessel wall necrosis. [136]. Urticarial vasculitis can present with prolonged wheals and angioedema lasting over 24 h. Diagnosis is confirmed through histological criteria, including fibrin deposits, leukocytoclasia, and extravasated erythrocytes, which are distinctive markers of this condition [137, 138]. Both long-lasting wheals (lasting more than 24 h) and angioedema can be caused by this condition. Histologically, CSU shows skin swelling and inflammation with eosinophils, neutrophils, lymphocytes, and nuclear debris, while vasculitis is rare in this context [61, 137].

Prevention and management of disease

Patient-reported outcome measures are essential tools for assessing CU activity and treatment effectiveness [139]. Prospective use of the Urticaria Activity Score (UAS) over seven days (UAS7) is considered the gold standard for evaluating CSU (number of wheals and itching sensations) [4, 140]. The Angioedema Activity Score (AAS) is a prospective tool resembling a diary, aiding clinicians in quantifying angioedema activity for patients with various recurrent angioedema forms [141]. Modified versions of the Urticaria Activity Score (UAS), such as the Cholinergic Urticaria Activity Score and the Cold Urticaria Activity Score, are utilised in collecting daily data for chronic inducible urticaria (CIndU). These scores assess the severity of wheals, itching, and trigger encounters within 24 h [139, 142, 143]. Retrospective tools with a 4-week recall time, such as the Urticaria Control Test (UCT) and the Angioedema Control Test (AECT), are used to evaluate the success of treatment in preventing disease flare-ups in all types of CU (Fig. 2)

Table 1 The list includes prospective molecular targets, therapeutic agents, class, route of administration, and clinical trial number (identification) in chronic urticaria

Therapeutic agents	Alternative names of the therapeutic agent	Class of therapeutic agents	Route of administration of the therapeutic agents	Molecular target of the therapeutic agent	Class of CU	Stage of clinical trial	NCT number registered in clinicaltrials.gov database
Quilizumab	Anti M1 prime monoclonal antibody; MEMP-1972A; RG-7449	mAB	S.C	IgE	CSU	Phase II	NCT01987947
Eculizumab	ABP 959; BEKEMV;	mAB	–	C5a inhibitor	CSU	Not applicable	[146]
LY 3454738	CD200R Antibody	mAB	IV	CD200R	CSU	Phase II	NCT04159701
MTPS9579A	RG-6173	mAB	IV	Tryptase	CSU	Phase II	NCT05129423
Canakinumab	ACZ-885, Anti-IL-1 beta monoclonal antibody; Antibody A; Ilaris	mAb	SC	IL-1β	CSU	Phase	NCT01635127
Dupilumab	Dupilumab-Sanofi/Regeneron; Dupixent; REGN-668; SAR-231893, BAT-2406	mAB	SC	IL-4Rα	CSU	Phase II–III	NCT03749135–NCT04180488
					CholU	Phase II	NCT03749148
					ColdU	Phase III	NCT04681729
Benralizumab	Benra, Benralizumab—AstraZeneca/Kyowa Hakko Kirin, Benralizumab—Kyowa-Hakko/AstraZeneca, BIW-8405, BIW-8405-IL-5R; Fasenra; KHK 4563; MEDI-563	mAb	SC	IL-5Rα	CSU	Phase II	NCT04612725
						Phase IV	NCT03183024
Mepolizumab	240,563; Bosatria; Mepolizamab; Nucala; SB-240563; BAT-2606	mAb	SC	IL-5	CSU	Phase I	NCT03494881
Vixarelimab	KPL-716; RG-6536; RO-7622888	mAb	SC	IL-31 (via OSMRβ)	CSU	Phase II	NCT03858634
Rituximab	IDEC-102; IDEC-C2B8; IDEC-C2B8-anti-CD20; MabThera; R 105; RG 105; Ristova; Rituxan; Rituximab-EU; RO-452294	mAb	IV	CD20	CSU	Phase I–II	NCT00216762
Ligelizumab	QGE-031	mAb	SC	FcεRI (via IgE)	CSU	Phase II	NCT02649218
							NCT02477332
						Phase III	NCT03580356
							NCT03580369
							NCT04210843
							NCT03907878
					CSU,CholU,ColdU	Phase I	NCT04513548
					ClndU	Phase III	NCT05024058

Table 1 (continued)

Therapeutic agents	Alternative names of the therapeutic agent	Class of therapeutic agents	Route of administration of the therapeutic agents	Molecular target of the therapeutic agent	Class of CU	Stage of clinical trial	NCT number registered in clinicaltrials.gov database
Barzolvolimab	CDX-0159	mAb	IV	KIT	CSU	Phase I	NCT04538794
						Phase II	NCT05368285
					ColdU, CholU, symptomatic dermographism	Phase I	NCT04548869
UB-221	–	mAb	IV	FcεRI (via IgE)	CSU	Phase I	NCT03632291
							NCT04175704
							NCT04404023
						Phase II	NCT05298215
Lirentelimab	AK 002; Antolimab	mAb	IV	Siglec 8	CSU, CholU, symptomatic dermographism	Phase II	NCT03436797
UCB8600	–	mAb	Oral	FcεRI (via IgE)	CSU	Phase I	NCT04444466
Reslizumab	–	mAbs	IV	anti-IL5	CSU, ColdU	-	[147]
Tezepelumab	AMG 157; MEDI-9929; Tezepelumab-ekko; Tezspire	mAb	SC	TSLP	CSU	Phase II	NCT04833855
GSK2646264	–	SM	Topical	SYK	CSU, ColdU	Phase I	NCT02424799
TAS5315	–	SM	Oral	BTK	CSU	Phase II	NCT05335499
Tirabrutinib	GS-4059; ONO-4059; Tirabutinib hydrochloride—Gilead Sciences/Ono Pharmaceutical; Velexbru	SM	Oral	BTK	CSU	Phase II	NCT04827589
Rilzabrutinib	PRN-1008; SAR-444671	SM	Oral	BTK	CSU	Phase II	NCT05107115
Remibrutinib	LOU-064; LOU064-NXA; NVP-LOU064-NXA	SM	Oral	BTK	CSU	Phase II	NCT03926611
							NCT04109313
						Phase III	NCT05048342
							NCT05032157
							NCT05030311
Fenebrutinib	GDC-0853; RG-7845; RO-7010939	SM	Oral	BTK	CSU	Phase II	NCT03137069
							NCT03693625
JW 1601	LEO-152020; LP-0190	SM	Oral	H4R	CholU	Phase II	NCT04853992

Table 1 (continued)

Therapeutic agents	Alternative names of the therapeutic agent	Class of therapeutic agents	Route of administration of the therapeutic agents	Molecular target of the therapeutic agent	Class of CU	Stage of clinical trial	NCT number registered in clinicaltrials.gov database
Etanercept	mAbx01; Enbrel; p75TNFR-Ig; rhu TNFR-Fc; Soluble tumour necrosis factor receptor p75 Fc IgG1 fusion protein; TNF receptor fusion protein; TNFR-Fc-p75; TNR-001	FP	SC	TNF	CSU	Phase II–III	NCT01030120
Rilonacept	ARCALYST; Arcalyst; IL-1-Cytokine-Trap; IL-1-Trap; Interleukin-1 Trap; KPL 914; RGN-303	FP	SC	IL-1β, IL-1α	ColdU	Phase II	NCT02171416
AZD1981	–	Antagonist	Oral	CRTh2	CSU	Phase II	NCT02031679

– = Not Reported"

[144, 145]. Several therapeutics in the management of CU are listed in Table 1.

Management

Second-generation antihistamines (sgAHs) that effectively block the H1 receptor are affordable and considered the primary treatment option for urticarial [148, 149]. Although they do not exhibit antagonistic effects on histamine binding, they function as inverse agonists, so shifting the equilibrium towards an inactive state [150]. The use of first-generation H1-AH is generally discouraged due to its sedative and anticholinergic properties, and its potential for drug-drug interactions [4, 151]. Systemic glucocorticoid hormones are efficacious in treating urticaria when administered at standard doses, but this effect is not seen universally [4]. However, a study revealed that a short course of oral corticosteroids such as prednisone, for a maximum of 10 days, can be beneficial in treating AU and acute exacerbations of CSU by reducing the duration of the illness [152–154]. The safety and efficacy of off-label high-dosage sgAH therapy, administered at a dosage up to four times the approved daily dose, has been shown for the following antihistamines: cetirizine, bilastine, desloratadine, ebastine, fexofenadine, levocetirizine, and rupatadine [155–161]. In the context of urticaria treatment, it is suggested to consider high-dose sgAHs as the first strategy when the standard dosage fails to control symptoms effectively. The optimal timing for adjusting the dosage of antihistamine medicine is decided by professional discretion, which may include gradual reduction or abrupt discontinuation. Based on half-life estimates, it is suggested that two weeks is sufficient to see changes in antihistamine levels in CU [161]. Omalizumab, the first monoclonal antibody targeting IgE, can decrease the levels of unbound IgE and modulate the expression of FcεRI on basophils and mast cells [162–165]. The downregulation of FcεRI expression can decrease cellular activation mediated by IgE and IgG anti-FcεRI antibodies, inhibiting the release of histamine and mitigating inflammation [165]. Substantial data have supported the use of Omalizumab as an adjunctive treatment to antihistamines and is highly recommended for patients aged 12 years and above with CSU [166]. Omalizumab has been shown to improve the quality of life in individuals with chronic spontaneous urticaria (CSU) in clinical trials and real-world studies [167–170].

Conclusion

In conclusion, chronic urticaria represents a diverse spectrum of CSU and CIndU conditions. This comprehensive overview of the article sheds light on the complex

interplay of cellular infiltration, immune responses, coagulation cascades, and autoantibodies underlying the pathophysiology of chronic urticaria. The intricate relationships between various immune cells, cytokines, autoantibodies, and triggers like histamine contribute to the persistent wheals and angioedema that characterize these conditions. Examining comorbidities associated with this condition emphasizes its systemic impact, including autoimmune disorders, infections, and mental health challenges. The concurrent existence of CIndU and CSU further underscores the need for a holistic diagnostic and therapeutic approach to address the complexity of triggers and symptoms. In management, the article highlights the pivotal role of assessment tools like UAS and AAS in measuring disease severity and guiding treatment strategies. The therapeutic options continue to expand from second-generation antihistamines to monoclonal antibodies. Omalizumab's emergence as an adjunctive treatment offers renewed hope, particularly for those who do not respond to traditional therapies. A list of potential molecular therapeutic targets and their targeting agents have been enlisted in Table 1, along with their NCT for identification. Understanding and managing chronic urticaria involves unravelling intricate immunological mechanisms, identifying relevant triggers, and addressing interconnected comorbidities. As research continues to uncover novel insights, healthcare providers are better equipped to provide accurate diagnoses, effective treatments, and improved quality of life for individuals battling chronic urticaria. A holistic approach encompassing immunology, neurobiology, and patient-centred care is essential in managing the diverse facets of this enigmatic condition.

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