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Updates on the Treatment and Management of Urticaria in 2025

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Chronic spontaneous urticaria (CSU) is increasingly recognized as a complex immune-mediated disorder, driven by interactions among T cells, mast cells, and inflammatory mediators. This paper summarizes the latest advances in urticaria treatment and management, incorporating new targeted therapies and evidence-based clinical guidelines.

Introduction

Chronic Urticaria (CU) is a long-lasting disease affecting up to 86 million people worldwide.[1,2] It is increasingly recognized as a complex immune-mediated disorder, driven by dysregulated interactions between mast cells, their receptors, mediators, activating signals, and T cells.[2] This growing evidence has laid the framework for more effective, targeted treatments with the final aim of achieving sustained disease control, and reducing the associated morbidity and mortality.[3] As of 2025, significant advancements have been made in the treatment and management of chronic spontaneous urticaria (CSU), with the incorporation of new targeted therapies. While second-generation H1-antihistamines remain the first-line treatment, new biologic agents, including interleukin (IL)-4Ra monoclonal antibodies such as dupilumab, and emerging Bruton's tyrosine kinase (BTK) inhibitors, such as remibrutinib, have demonstrated efficacy in refractory cases.[4-6] This review synthesizes findings from controlled clinical trials and real-world applications to present an evidence-based perspective on the evolving landscape of CSU management, focusing on advancements in targeted biologic therapies, immunomodulatory strategies, and precision medicine approaches.

Methods

A systematic literature search was conducted across major medical and scientific databases, including PubMed, Scopus, and Web of Science, using relevant keywords such as ("Chronic Urticaria"[Mesh]) AND ("Biological Therapy"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Janus Kinases"[Mesh] OR "Treatment Outcome"[Mesh])" for studies published between 2023 and January 2025. The selection criteria included randomized controlled trials and real-world cohort studies published in peer-reviewed journals. In ClinicalTrials.gov, we set the condition/disease as "Chronic Urticaria", other terms "Hives", all ages, all sex, and the study phase including early phase 1 through phase 4.

Results

A total of 406 studies were retrieved from medical scientific databases, alongside 185 clinical trials registered on clinicaltrials.gov. These included two in early phase 1, 27 in phase 1, 73 in phase 2, 62 in phase 3, and 21 in phase 4. The key findings are presented below, with further details provided in **Tables 1 and 2**.

Advances in Pathogenesis and Immunologic Understanding

The immunologic mechanisms involved in CU include:

1. Mast cell activation and degranulation: Occurs through the stimulation of their receptors (KIT [CD117], FcεRI, Mas-related G-protein-coupled receptor X2 [MRGPRX2], component 5a receptor [C5aR], protease-activated receptor [PAR]1, PAR2) or the inhibition of their negative receptors (sialic acid-binding immunoglobulin-like lectin-8 [SIGLEC-8], sialic acid-binding immunoglobulin-like lectin-6 [SIGLEC-6], CD200R, CD300a). This ultimately results in the release of potent mediators and chemokines such as IL-4, IL-5, IL-13, IL-17, IL-31, tryptase, prostaglandin D2 (PGD2), eotaxins, monocyte chemotactic protein-3 (MCP3), regulated upon activation, normal T-cell expressed and secreted (RANTES), platelet-activating factor (PAF), C3a, C5a, and tumour necrosis factor (TNF), or the activation of signalling pathways (for example, BTK, Janus kinase inhibitor [JAK], and spleen tyrosine kinase [SYK]).[7]
2. Cellular infiltrates: Involves the activation of eosinophils, such as Major Basic Protein (MBP), basophils, and various T-cell subsets (Th2, Th1, Th17).[8,9]
3. Coagulation and complement activation: The tissue factor produced by eosinophils triggers the coagulation cascade and complement system. This ultimately leads to the activation of coagulation factors X and II, which causes the degranulation of mast cells and basophils.[10]
4. Autoantibodies: In the context of autoimmune urticaria, immunoglobulin (Ig)E may bind to the α subunit of FcεRI. Additionally, IgG-anti-IgE, IgG-anti-IL-24, and IgE-anti-thyroid peroxidase (TPO) have also been discovered.[11]
5. Neurogenic inflammation: Activation of histamine, IL-31, neuropeptides, and MRGPRX2 contributes to the inflammation of sensory nerves, as well as pruritus and urticaria symptoms.[12]

Updated Therapeutic Strategies for CSU

First-Line Treatment: Second-Generation H1-Antihistamines (sgAHs)

Current guidelines recommend starting treatment with standard-dose sgAHs, which are effective in approximately half of patients. If symptom control is inadequate, the dose may be increased up to fourfold if necessary, leading to symptom control in up to 63% of cases.[13,14] No additional benefit was observed when combining different sgAHs.[15]

Biologic Therapies

Omalizumab: This anti-IgE monoclonal antibody (mAb) remains the preferred first-line add-on therapy for patients unresponsive to high-dose sgAHs. Studies have confirmed rapid symptom relief with dose adjustments improving response rates across various age groups, including children, adolescents, and older adults.[16,17]

Dupilumab: This anti-IL-4Rα mAb has demonstrated significant reductions in urticaria activity (UAS7) in the LIBERTY-CSU CUPID trials, particularly among biologic-naïve CSU patients. Nonetheless, while patients who failed to respond

Mechanism	Molecule	Clinical Trial identifier	Phase	Status	Route of Administration	Study Name	Notes
Anti-IgE mAb	Omalizumab	NCT01287117, NCT01292473, NCT01264939	4	Complete	Subcutaneous	GLACIAL, ASTERIA	
Anti-IgE mAb	LP-003	NCT06228560	2	Recruiting	Subcutaneous		
Anti-IgE mAb	JYB1904	NCT06509334	2	Recruiting	Subcutaneous		
Anti-IgE mAb	UB-221	NCT04404023, NCT04175704, NCT03632291	2	Not yet recruiting	IV infusion		
Anti-IL-4r mAb	Dupilumab	NCT04180488	3	Complete	Subcutaneous	LIBERTY-CSU CUPID	
Anti-KIT	Barzolvolimab	NCT06445023, NCT06455202	3	Recruiting	Subcutaneous	EMBARQ-CSU1, EMBARQ-CSU2	
Anti-KIT	Briquilimab	NCT06736262, NCT06162728, NCT06736262	2	Recruiting	Subcutaneous	BEACON study	
BTK inhibitor	HWH486	NCT06295302	2a	Recruiting	Oral		No results yet
BTK inhibitor	TAS5315	NCT05335499	2a	Complete	Oral		No results yet
BTK inhibitor	Remibrutinib	NCT05030311, NCT05032157	3	Complete	Oral	REMIX-1, REMIX-2	
BTK inhibitor	Rilzabrutinib	NCT05107115	2	Complete	Oral	RILECSU	
BTK inhibitor	HS-10561	NCT06864507	1 and 2	Not yet recruiting	Oral		
C5aR inhibitor	INF904	NCT06555328	2	Recruiting	Oral		No results yet
CRTh2 antagonist	AZD1981	NCT02031679	2	Complete	Oral		Good results but no conclusions could be made due to the small sample size
IgE fusion protein	YH35324	NCT05960708	1	Complete	Subcutaneous		
IL-5 mAb	Mepolizumab	NCT03494881	1	Complete	Subcutaneous		

Mechanism	Molecule	Clinical Trial identifier	Phase	Status	Route of Administration	Study Name	Notes
JAK1 inhibitor	Porvocitinib	NCT05936567	2	Not yet recruiting	Oral		
JAK3/TEC inhibitor	Ritlecitinib (PF-06651600)	NCT06795373	2	Recruiting	Oral		
MRGPRX2 antagonism	EP262	NCT06050928, NCT06077773	2	Recruiting	Oral	CALM-CSU	No results yet
MRGPRX2 antagonism	EVO756	NCT06603220	2	Recruiting	Oral		
SYK inhibitor	GSK2646264	NCT02424799	1	Unknown	Topical		It was well tolerated but no conclusions could be made about changes in the urticaria activity score due to the low number of CSU patients recruited
TYK2/JAK1 inhibitor	TLL-018	NCT05373355, NCT06396026	3	Recruiting	Oral		

Table 1. Overview of Emerging Promising Therapeutic Agents for Chronic Spontaneous Urticaria that are Under Clinical Investigation; *courtesy of Karla Robles-Velasco, MD, Veronica Ferris Pasquini, MD, Patryck Pontes, MD, and Hermenio Lima, MD*.

Abbreviations: BTK: Bruton's tyrosine kinase; **CRTH2:** Chemoattractant receptor-homologous molecule expressed on Th2 cells; **C5aR:** Component 5a receptor; **mAb:** Monoclonal antibody; **MRGPRX2:** Mas-related G-protein-coupled receptor X2; **JAK1:** Janus kinase 1 inhibitor; **JAK3/TEC:** Janus kinase 3/Tyrosine kinase expressed in hepatocellular carcinoma; **TYK2:** Tyrosine kinase 2.

Mechanism	Molecule	Clinical Trial Identifier	Phase	Status	Notes
Anti CD80/CD86 - CD28	Abatacept	NCT00886795	1 & 2	Unknown	Pilot study with good results but no conclusions could be made due to the small sample size.
Anti-IgE mAb	Ligelizumab	NCT05024058, NCT04210843	3	Terminated	Phase III PEARL studies (CQGE031C2302 and CQGE031C2303) with ligelizumab met their primary endpoint of superiority vs. placebo at week 12 for CSU treatment, but not vs. omalizumab. The decision to discontinue was not based on safety concerns.
Anti-IgE mAb	UCB8600	NCT04444466	1	Terminated	Terminated due to internal company decision; not safety related.
Anti-IL5R alpha mAb	Benralizumab	NCT04612725	2b	Terminated	Study did not meet its primary endpoint.
Anti-KIT	THB001	NCT05510843	1	Terminated	The decision to discontinue the study was made after observing moderate drug induced liver injury in two participants enrolled in the first dose cohort.
Anti-Siglec-6 mAb	AK006	NCT06577116, NCT06072157	1	Terminated	AK006 did not demonstrate therapeutic activity in CSU.
Anti-Siglec-8 mAb	AK002 (Lirentelimab)	NCT05528861, NCT03436797	2	Terminated	Study did not meet its primary endpoints.
BTK inhibitor	Fenebrutinib	NCT03693625	2	Terminated	Recruitment was stopped after an interim analysis of the study data.
BTK inhibitor	Tirabrutinib	NCT04827589	2	Withdrawn	Development program was terminated.
C5aR	Avdoralimab	EudraCT No. 2020-002510-40	2	Terminated	Prematurely ended.
CD200R agonist	LY3454738	NCT04159701	2	Terminated	The study was terminated for lack of efficacy after an interim analysis was performed.
IL-1β	Canakinumab	NCT01635127	2	Unknown	Lack of efficacy in treating adult patients with moderate to severe CSU.
IL-31 (via OSMRβ)	KPL-716 (Vixarelimab)	NCT03858634	2	Complete	Results posted in clinicaltrials.gov showed no differences from placebo.
Tryptase inhibitor	MTPS9579A	NCT05129423	2	Withdrawn	Development of MTPS9579A was terminated for strategic/ business reasons.
TSLP antagonist	Tezepelumab	NCT04833855	2b	Complete	Study did not achieve its primary endpoint.

Table 2. Investigational Therapies for Chronic Spontaneous Urticaria That Failed to Demonstrate Clinical Benefit or Were Discontinued; *courtesy of Karla Robles-Velasco, MD, Veronica Ferris Pasquini, MD, Patryck Pontes, MD, and Hermenio Lima, MD.*

Abbreviations: BTK: Bruton's tyrosine kinase; **C5aR:** Component 5a receptor; **IgE:** Immunoglobulin E; **IL5R:** Interleukin 5 receptor; **mAb:** Monoclonal Antibody; **OSMRβ:** oncostatin M receptor-β; **SIGLEC-6:** Sialic acid-binding immunoglobulin-like lectin-6; **SIGLEC-8:** Sialic acid-binding immunoglobulin-like lectin-8.

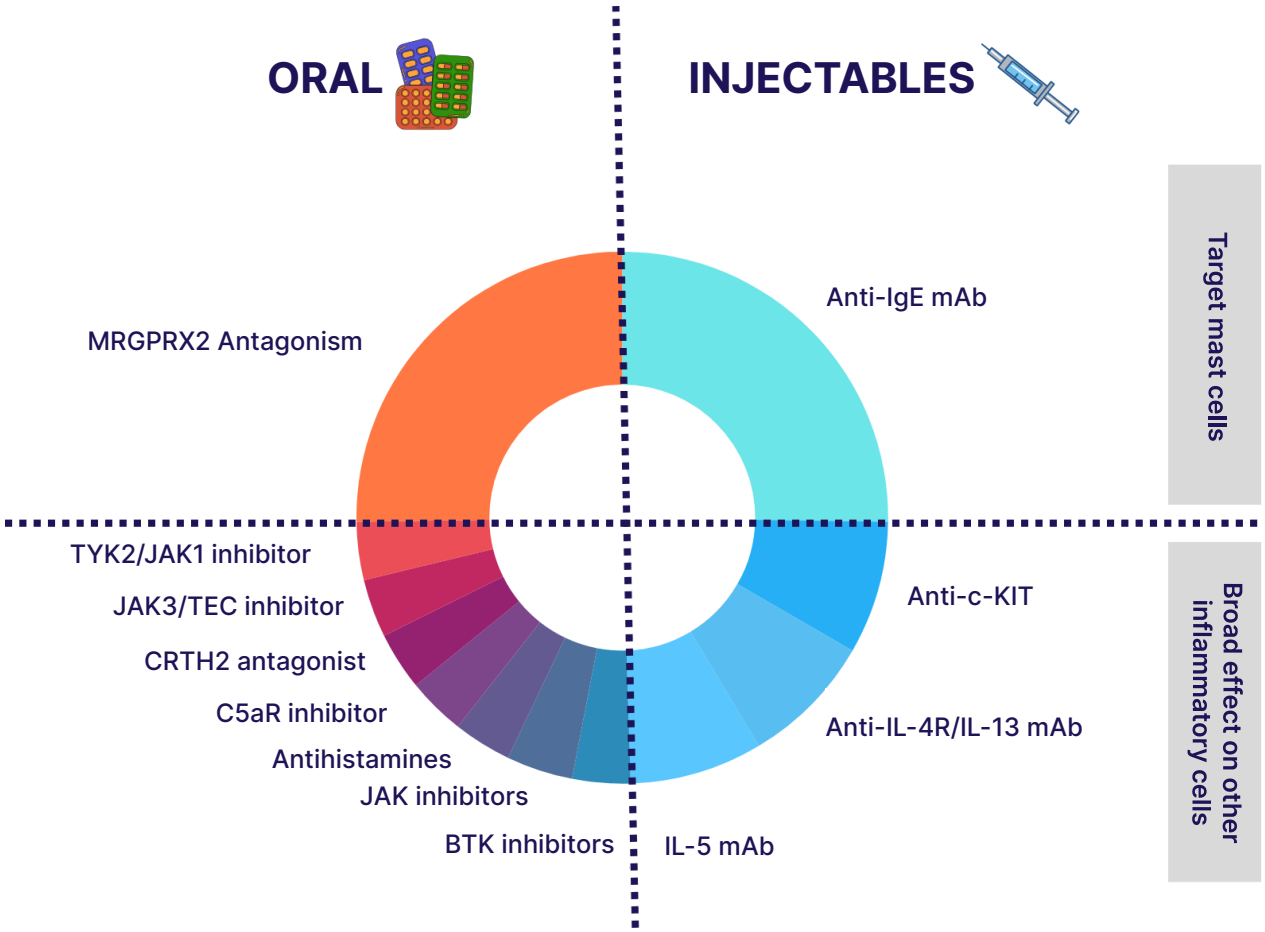

Figure 1. Overview of therapeutic strategies for Chronic Spontaneous Urticaria (CSU), categorized by route of administration, mechanism of action, and immunological target. The circular diagram segments include available and emerging treatments based on whether they are administered orally (left half) or via injection (right half). Therapeutic classes include MRGPRX2 antagonists, BTK and JAK inhibitors, anti-IgE therapies, anti-cytokine agents (targeting IL-4, IL-5, and IL-13), and mast cell-targeting antibodies such as anti-c-KIT. Vertical axis represents the target of action—from direct mast cell modulation (top) to broader anti-inflammatory effects (bottom); *courtesy of Karla Robles-Velasco, MD, Veronica Ferris Pasquini, MD, Patryck Pontes, MD, and Hermenio Lima, MD.*

Abbreviations: BTK: Bruton's tyrosine kinase; **CRTH2:** Chemoattractant Receptor-homologous molecule expressed on Th2 cells; **C5aR:** Component 5a receptor; **IL:** interleukin; **JAK1:** Janus kinase 1 inhibitor; **JAK3/TEC:** Janus kinase 3/Tyrosine kinase expressed in hepatocellular carcinoma; **mAb:** Monoclonal antibody; **MRGPRX2:** Mas-related G-protein-coupled receptor X2; **TYK2:** Tyrosine kinase 2.

to omalizumab exhibited positive results with dupilumab, the phase 3 study did not achieve its primary endpoint in this subset.[6] Dupilumab is now approved for CSU treatment in Japan, the United Arab Emirates, Brazil, and the United States, and is currently undergoing evaluation in the European Union.[18]

Ligelizumab: This high-affinity monoclonal anti-IgE antibody was evaluated in the phase 3 PEARL 1 and PEARL 2 trials. While it showed improvement of CSU symptoms compared to placebo, it did not show superiority over omalizumab. Consequently, its development for CSU was discontinued. Nonetheless, ligelizumab's higher affinity for IgE and favourable safety profile suggest potential utility for use in other IgE-mediated conditions.[19]

LP-003: This novel high-affinity, long-acting anti-IgE antibody has shown non-inferiority to

omalizumab in reducing the UAS7, based on an interim analysis of the phase 2 study.[20]

JYB1904: Currently in phase 2, this anti-IgE mAb is actively recruiting patients for assessing its efficacy, safety and tolerability.[21]

UB-221: This is an IgG1 mAB that targets the Cε3 domain of IgE. Although its phase 1 trial (NCT03632291) was completed, no results have been posted on its efficacy or safety. A phase 2 trial is currently recruiting participants (NCT05298215).

Mepolizumab: This anti-IL5 mAb works by reducing eosinophil accumulation and activation. A phase 1 trial was completed but results have not yet been posted.[22]

Tezepelumab: This is a high-affinity humanized IgG2 mAb against thymic stromal lymphopoietin (TSLP). The phase 2b INCEPTION study showed that the primary endpoint of UAS7 change at week 16 was not met compared to placebo. However, greater improvement was observed in anti-IgE–naïve patients, with a delayed, sustained reduction in CSU activity through week 32, particularly in those with lower baseline IgE levels and longer disease duration, suggesting a potential long-term TSLP blockade effect.[23]

Vixarelimab (KPL-716, NCT03858634): This human mAb targets the oncostatin M receptor β and IL-31. Phase 2 trial results showed no differences in outcomes compared to placebo.[24]

IgE Fusion Protein

YH35324: This long-acting IgETrap-Fc protein showed a favourable safety profile, dose-dependent exposure, and greater suppression of serum-free IgE levels compared to omalizumab. In a clinical study, higher rates of complete and well-controlled CSU were observed in the YH35324 6 mg/kg group, demonstrating its superior therapeutic potential over omalizumab.[25]

MRGPRX2 Antagonists

EVO756: This MRGPRX2 antagonist targets mast cell-neuron interactions.[26] Phase 1 trial results demonstrated that EVO756 was a well-tolerated oral therapy that showed effective target engagement in CSU. A phase 2 trial (NCT06603220) is currently underway to further evaluate its safety and efficacy in Chronic Inducible Urticaria (CIndU).[27]

EP262: This agent has completed a phase 1b trial for CIndU, though results are pending.[28] In addition, a phase 2 study (CALM-CSU) (NCT06077773) is currently active and recruiting participants with CSU.[29]

Anti-c-KIT Monoclonal Antibodies

Barzolvolimab: This anti-c-KIT mAb has shown promising results in phase 2 trials. In patients with antihistamine-refractory CSU, treatment with 150 mg every 4 weeks and 300 mg every 8 weeks demonstrated significant improvements in UAS7 scores at 12 weeks, showing clinically meaningful reductions versus placebo. Among CIndU patients, this therapy led to a 95% complete response rate and improved urticaria control. Barzolvolimab was well tolerated in both populations, with benefits including mast cell depletion in the skin, reduced tryptase levels, and enhanced quality of life.[30]

Briquilimab: Initial findings from the phase 1b/2a study involving 47 participants indicate a low incidence of adverse events of mild severity related to c-KIT-expressing tissues. No changes in hair or skin pigmentation were observed, and mild taste changes were noted mainly after the first dose. A limited number of cases of low-grade neutropenia were reported but resolved without requiring treatment interruption. The pharmacokinetic results align with predictions, and full study data is expected in 2026.[31,32]

Bruton's Tyrosine Kinase Inhibitors

Remibrutinib: The phase 3 REMIX-1 and REMIX-2 trials assessed oral remibrutinib (25 mg twice daily) in 925 patients. At week 12, remibrutinib significantly improved UAS7 scores compared to placebo and achieved higher rates of UAS7 ≤6 (~48% vs. ~22%) and complete response (~30% vs. ~8%). These benefits were sustained through week 24 ($P < 0.001$). Adverse events were similar between groups, though petechiae occurred more frequently in the remibrutinib group (3.8% vs. 0.3%). These findings confirm remibrutinib's strong efficacy and favourable safety profile (NCT05030311, NCT05032157),[5] positioning it as a promising alternative for patients who are unresponsive to omalizumab and dupilumab.

TAS5315: This BTK inhibitor, which also exhibits IL2-inducible T-cell kinase (ITK) inhibitory activity,[33] was evaluated in a clinical trial of 126 patients with CSU. At week 12, TAS5315 (doses ranging from 0.25–4 mg) showed greater reductions in HSS7 scores (-5.10 to -9.55) compared to placebo (-4.34). The highest rate of no-hives (HSS7=0) was observed in the 4 mg

group (47.1%), with 50% of these responders maintaining a no-hives status through week 20. Petechiae were the most common adverse event, though they were mild. TAS5315 demonstrated prolonged CSU improvement beyond treatment discontinuation, making it a potential option for patients unresponsive to H1-antihistamines.[33,34]

HWH486: In a phase 1 study of 96 participants, 44 adverse events were reported, 31.2% of which were treatment-emergent adverse events in the HWH486 group and 25% in the placebo group. Most adverse events were mild, (grade 1) except for one case of grade 2 anemia. No major adverse events, withdrawals, or deaths occurred. Overall, the incidence of adverse events was similar between HWH486 and placebo groups (P =0.77, P =1.00), except for a significant difference observed across the 50, 100, 200, 400, and 800 mg groups (P =0.03). The findings support a favourable safety profile for HWH486.[35]

Rilzabrutinib: The phase 2 RILECSU trial[36] showed that rilzabrutinib significantly reduced UAS7 and itch severity score over 7 days (ISS7) scores in CSU patients uncontrolled with H1-antihistamines, with improvements observed as early as week 1 and sustained through week 12 (P <0.02). A 52-week follow-up study confirmed ISS7 reductions across subgroups. Additionally, rilzabrutinib was shown to reduce IgG anti-FcεRI autoantibodies, suggesting reduced mast cell and basophil activation. The treatment was well tolerated, with headache, nausea, and diarrhea as the most commonly reported side effects, supporting it as a promising CSU treatment.[37,38]

Spleen Tyrosine Kinase Inhibitor

GSK2646264: This phase 1/1b study evaluated GSK2646264 cream in healthy volunteers and patients with Cold Urticaria (ColdU) or CSU. The cream was well tolerated. In ColdU patients, it reduced the critical temperature threshold in four out of nine patients. However, due to the small sample size, no conclusions could be drawn regarding its efficacy for CSU.[39]

Janus Kinase Inhibitors

Povorcitinib (JAK 1 inhibitor): This agent is currently being evaluated in a phase 2 study, which is active but not yet recruiting.[40]

Ritlecitinib (JAK3/Tyrosine-kinase (TEC) inhibitor): Also known as PF-06651600, is a recently discovered JAK3 inhibitor with selectivity for JAK3 over the other three JAK isoforms. PF-06651600 also irreversibly inhibits the TEC kinase family (BTK, bone marrow tyrosine kinase on chromosome X [BMX], ITK, resting lymphocyte kinase [RLK], TEC). It is currently in a phase 2 study, and actively recruiting participants.

TLL-018 (Tyrosine kinase 2 inhibitors (TYK2)/Janus kinase 1 inhibitor): This dual TYK2/JAK1 inhibitor has shown strong efficacy in patients with moderate-to-severe CSU who are unresponsive to antihistamines. In a 41-patient trial, significant improvements in UAS7 and ISS7 scores were observed by week 4 and were sustained through week 12 (P <0.01). At week 12, up to 64.3% of patients achieved a UAS7 score of zero. Reported adverse events were mild to moderate across all groups.[41] A phase 3 trial is currently ongoing.[42]

Component 5a Receptor (C5aR) Inhibitor

INF904: In phase 1 studies, INF904 showed good tolerability and safety across doses ranging from 3 mg to 240 mg. It achieved a ≥90% blockade of C5a-induced neutrophil activation over 14 days, highlighting its potential to disrupt inflammatory processes. A phase 2 study is currently recruiting participants.[43]

Third-Line Therapy: Cyclosporine A and Off-Label Agents

Cyclosporine A: Recommended only after failure of omalizumab, dupilumab, or remibrutinib. Cyclosporine A provides potent immunosuppressive action, but long-term safety remains a concern.

Off-label Therapies for Refractory CSU

In clinical practice, following failure of omalizumab at 300 mg subcutaneously every 4 weeks, a stepwise, individualized approach is recommended. This may include increasing omalizumab to 450 mg or 600 mg every 4 weeks, or shortening the dosing interval to every 2 weeks, as supported by real-world and expert consensus data. For patients who remain uncontrolled despite optimized omalizumab therapy, consideration should be given to transitioning to alternative biologic or small-molecule agents, such as dupilumab or remibrutinib, where available, or to well-established off-label immunomodulatory therapies.

For patients with difficult-to-treat CSU, dapsone, hydroxychloroquine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin (IVIG), and rituximab are being

explored. Additionally, emerging biologics such as fenebrutinib,[44] reslizumab,[45] and mepolizumab,[22] have shown promising results but require further study.

Discussion and Conclusions

Recent advances in CSU treatment indicate a shift toward precision medicine and targeted immunologic treatments. While high-dose second-generation H1-antihistamines remain the cornerstone of first-line treatment, the introduction of novel biologics (dupilumab) and BTK inhibitors (remibrutinib) has expanded therapeutic options, particularly for patients with refractory disease. These advances are supported by a better understanding of CSU pathogenesis, which includes mast cell signalling, autoimmune mechanisms, and neurogenic inflammation. Although these therapies show promise, many of the novel drugs presented remain in early stages of clinical development. Further study is needed to determine their long-term safety, cost-effectiveness, and optimal patient selection criteria. The implementation of these new medicines into clinical practice must be supported by strong, evidence-based guidelines that consider both clinical efficacy and patient-centred outcomes.

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