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LEADING ARTICLE

Update on the Treatment of Chronic Spontaneous Urticaria

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Abstract

Chronic spontaneous urticaria (CSU) is a mast cell-mediated skin disease that presents with wheals, angioedema, or both for more than 6 weeks. Less than 10% of patients have complete control of their CSU (the main goal of CSU treatment) with second generation H1-antihistamines, the first-line treatment. About 70% of patients with antihistamine-refractory CSU do not reach complete control with omalizumab, the second-line treatment. Novel therapies are especially needed for patients with mast cell-activating immunoglobulin (Ig)G autoantibodies (autoimmune CSU) associated with nonresponse or late response to omalizumab. Furthermore, there is a lack of disease-modifying treatments that induce long-term CSU remission after drug withdrawal. Several emerging treatments can address these unmet needs including Bruton tyrosine kinase inhibitors, e.g., remibrutinib and rilzabrutinib; anti-KIT monoclonal antibodies, e.g., barzolvolimab; and anti-cytokine therapies, e.g., dupilumab. In clinical trials, 30–31%, 28–32%, and 38–51% of patients with CSU showed complete response to treatment with dupilumab (phase 3, week 24), remibrutinib (phase 3, week 24), and barzolvolimab (phase 2, week 12), respectively. The most common adverse events were injection site reactions for dupilumab (12%), respiratory tract infections (11%), headache (6%), and petechiae (4%) for remibrutinib and changes in hair color (14%), neutropenia / decreased neutrophil count (9%) and skin hypopigmentation (1%) for barzolvolimab. This review provides an update on the current state of development of treatments for CSU.

Key Points

Chronic spontaneous urticaria is a difficult-to-treat disease, with many patients failing to achieve complete disease control with second-generation H1-antihistamines and the anti-IgE antibody omalizumab.

Remibrutinib, a Bruton tyrosine kinase inhibitor, and the anti-IL-4Rα antibody dupilumab are effective and safe for treating chronic spontaneous urticaria and are expected to receive approval for this indication.

Other promising treatments in development for CSU include anti-KIT antibodies, e.g., barzolvolimab, JAK inhibitors, and MRGPRX2 antagonists.

1 Introduction

Chronic spontaneous urticaria (CSU) is a mast cell (MC)-mediated skin disease characterized by the unpredictable occurrence of itchy wheals (also called hives), angioedema, or both for more than 6 weeks [1–3]. CSU affects about 1% of the general population [4] and lasts for more than 1 year in more than 80% of patients [5]. In about 40% of patients, CSU has a large or extremely large impact on patient's quality of life [6]. CSU is a frustrating, unpredictable condition with a significant emotional burden, high rates of comorbidities such as anxiety and depression, sleep disorders, sexual dysfunction, and marked limitations and interference with work, school, family life, and social functioning [7, 8]. The economic cost and loss to patients and society due to CSU is considerable [9, 10].

The need for effective treatment of CSU is high, [11, 12] and complete protection from wheals and angioedema is the goal of treatment according to the international urticaria guideline [2]. Complete disease control (Urticaria Control Test [UCT] score of 16) and well-controlled CSU (UCT score of 12–15) with second

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generation H1-antihistamines (sgAHs) in licensed doses and updosed, the first-line treatment, is seen in about 7% and 21% of patients, respectively [11]. About 30% of patients with antihistamine-refractory CSU (e.g., defined as UCT < 11) have complete control with omalizumab, the second-line treatment [11, 13]. Cyclosporine A, the recommended third-line treatment, can result in an improvement in clinical score of > 90% in up to 100% of antihistamine-refractory patients (< 50% in most studies), but comes with many safety concerns including arterial hypertension, renal dysfunction, and broad immune suppression [11, 14]. Novel and more effective safe therapies are urgently needed.

Several novel treatments for these subpopulations of patients with CSU targeting different mechanisms involved in CSU are currently in various stages of development. While for some drugs the CSU programs have recently been stopped because they were not superior to current treatment options (ligelizumab) [15], or because of futility (benralizumab [16] and lirentelimab), others have just recently become available (dupilumab) or are in later stages of development, for example, Bruton's tyrosine kinase (BTK) inhibitors, KIT-targeted treatments, and Janus kinase inhibitors [17]. This review presents an update on difficult-to-treat patient populations (Table 1) and the phase 2 and phase 3 development programs for emerging drugs for the treatment of these and other CSU patient populations. We first review therapies that are expected to be available soon, followed by promising drugs which will probably become available mid- or long-term (Table 2).

2 Which Patient Populations Would Benefit Most from Novel Therapies?

2.1 Nonresponders to the First- and Second-Line Treatment

This group of patients are largely patients with autoimmune CSU (aiCSU) who make up at least 8% [18] and up to 69% [19] of all patients with CSU. This endotype is associated with MC-activating immunoglobulin (Ig)G autoantibodies against high-affinity IgE receptor (FcεRI)/IgE. AiCSU is characterized by high disease activity, autoimmune comorbidities such as Hashimoto's thyroiditis and vitiligo, low total IgE levels, and poor response to antihistamines and omalizumab [19].

2.2 Late Responders to Omalizumab

This is a subgroup of patients (about 16% [20]) who respond to omalizumab only after 2–5 months of treatment. Late/slow response was linked to aiCSU features such as low IgE and chronic urticaria index positivity [20]. Presence of IgE autoantibodies such as IgE-anti-TPO in many patients with aiCSU might explain why these patients respond to anti-IgE therapies, although more slower, in contrast to the "pure" IgG-mediated aiCSU [21, 22].

2.3 Patients with CSU Who Have Comorbidities

These patients could benefit from treatments targeting more than one disease. For example, inhibition of BTK can improve autoimmune diseases by reducing IgG autoantibody

Table 1 Subpopulations of patients with CSU which can benefit from novel treatments

Subpopulation [article section]	Response		Possible endotypes	Available treatments	New treatments
	sgAH	Omalizumab			
Nonresponders to the first- and second-line treatment [2.1]	–	–	IgG-mediated autoimmune CSU	Cyclosporine A	BTKi, anti-KIT
Late responders to omalizumab [2.2]	–	After 2–5 months of treatment	IgE- and IgG-mediated autoimmune CSU (overlap)	↑ dose of OMA or + cyclosporine A	BTKi, anti-KIT, dupilumab
Patients who have comorbidities [2.3]	–/+	–/+	CSU with comorbidities	sgAH, OMA	Allergy, CIndU: dupilumab, anti-KIT Autoimmune diseases: BTKi
Patients with likely long-lasting course of disease [2.4]	–/+	–/+	Long-lasting CSU	Probably cyclosporine A*	Probably BTKi, dupilumab*

BTKi Bruton tyrosine kinase inhibitors, *CIndU* chronic inducible urticaria, *CSU* chronic spontaneous urticaria, *OMA* omalizumab, *sgAH* second generarion H1-antihistamine, * potential for disease modification, – usually no response to this treatment, –/+ response to this treatment is possible

Table 2 Emerging drugs in phase 2 and 3 development for chronic spontaneous urticaria

Drug	Target	Type	Route	Phase	ClinicalTrials.gov identifier	Status, comments
Dupilumab	IL-4Rα	mAb	SC	2	NCT03749135	Completed
				3	NCT05526521	Recruiting
					NCT04180488	Active, not recruiting
Remibrutinib	BTK	SM	Oral	2	NCT03926611	Completed
					NCT04109313	Completed
				3	NCT05048342	Completed
					NCT05032157	Completed
					NCT05030311	Completed
					NCT05795153	Completed
					NCT05677451	Recruiting
				3b	NCT05513001	Active, not recruiting
					NCT06042478	Recruiting
Rilzabrutinib	BTK	SM	Oral	2	NCT05107115	Completed
TAS5315	BTK	SM	Oral	2	NCT05335499	Completed
Barzolvolimab	KIT	mAb	IV, SC	2	NCT05368285	Active, not recruiting
				3	NCT06445023	Recruiting
					NCT06455202	Recruiting
Briquilimab	KIT	mAb	SC	1b/2a	NCT06162728	Recruiting
Povorcitinib	JAK	SM	Oral	2	NCT05936567	Recruiting
TLL018	Dual JAK1/TYK2 inhibitor	SM	Oral	3	NCT06396026	Not yet recruiting
EP262	MRGPRX2	SM	Oral	2	NCT06077773	Recruiting
AK006	Siglec-6	mAb	IV, SC	1	NCT06072157	Recruiting
					NCT06577116	Enrolling by invitation
INF904	C5aR	SM	Oral	2	NCT06555328	Not yet recruiting

ClinicalTrials.gov data accessed on 16 November 2024

IV intravenous injection, *mAb* monoclonal antibody, *SC* subcutaneous injection, *SM* small molecule drug

production (i.e., multiple sclerosis), and blocking interleukin 4 receptor α (IL-4Rα) can also improve other type 2 inflammatory diseases such as asthma, chronic rhinosinusitis with nasal polyps, or atopic dermatitis [23].

2.4 Patients with CSU with a Likely Long-Lasting Course of Disease

In these patients, a disease modifying treatment could induce long-term disease remission.

3 Anti-IL-4Rα

Type 2 inflammation, characterized by the contribution of MC, activated Th2 cells, and the effects of cytokines such as interleukin (IL)-4 and IL-13, plays a substantial role in CSU [17]. IL-4 and IL-13 are primarily produced by T cells, MCs, and basophils [24, 25]. IL-13 partially shares signaling pathways with IL-4 owing to the common receptor, IL4-Rα on MCs, certain subsets of T cells, B cells, and monocytes [26–29]. IL-4 plays a central role in regulating the differentiation of antigen-stimulated naive T cells to Th2 cells. IL-4 also determines the B cell switch towards IgE and IgG4 production [28, 30] and promotes IL-13 production and degranulation of MC [24, 31]. Studies reported increased levels of IL-4 in the serum or plasma of patients with CSU [32, 33] comparable to those in atopic subjects [32], and there is significant expression of IL-4 in CSU skin lesions [34, 35]. Studies demonstrated higher levels of IL-13 in patients with autologous serum skin test (ASST, a marker of autoimmune CSU) positive CSU compared with both ASST-negative individuals and healthy controls [36, 37]. Analysis of transcriptomic data revealed upregulation of Th2-related (IL-4/IL-13 signaling) and Th17-related (IL-17/23 signaling) pathways in the lesional CSU skin compared with nonlesional and healthy control samples [38]. IL-4 and IL-13 may contribute to CSU pathophysiology via the stimulation of IgE and auto-IgE and auto-IgG production, activation of cutaneous

nerve fibres, and/or increasing sensitivity of MC to other stimuli such as MRGPRX2 agonists.

Dupilumab is a monoclonal antibody that blocks IL4-Rα, thereby inhibiting signaling of both IL-4 and IL-13. LIBERTY-CSU CUPID A and B are two randomized placebo-controlled phase 3 trials, sharing identical designs but involving distinct populations with CSU refractory to different prior therapies. In CUPID A, 138 patients aged 6 years and above with antihistamine-refractory, omalizumab-naive CSU were investigated, whereas CUPID B included 108 patients with CSU aged 12–80 years who were intolerant or had an incomplete or nonresponse to omalizumab [39]. Both studies consisted of a 24-week treatment period followed by a 12-week post-treatment observation period. Adults and adolescents ≥ 60 kg and children ≥ 15 kg and < 30 kg received a loading dose of dupilumab 600 mg, followed by 300 mg every 2 (every 4 weeks for children) weeks (q2w) or matched placebo following the same schedule. Adolescents < 60 kg and children ≥ 30 kg received a loading dose of dupilumab 400 mg followed by 200 mg q2w. Depending on regional regulatory requirements, the primary and key secondary endpoints were changes from baseline to week 24 in Weekly Urticaria Activity Score (UAS7) and Weekly Itch Severity Score (ISS7), respectively, or vice versa.

In CUPID A, both endpoints, UAS7 and ISS7, statistically significantly improved with dupilumab compared with placebo (difference −8.5 and −4.2 points, respectively). In addition, more patients achieved complete response to treatment (UAS7 = 0) with dupilumab than placebo (31.4% versus 13.2%, OR = 2.9 [1.2–7.2], $p = 0.0199$, Table 3) and experienced a ≥ 5-point reduction in ISS7, a minimally important difference (72.9% versus 42.6%, OR = 3.4 [1.6–7.3], $p = 0.0014$). In CUPID B, the change in UAS7 was statistically significant (EU hierarchy)/nominally significant (non-EU hierarchy); ISS7 at week 24 did not meet significance; and Weekly Hive Severity Score (HSS7) at week 24 was nominally significant. The number of complete responders was similar, with 13.0% versus 9.3% of dupilumab- versus placebo-treated patients achieving complete CSU control at week 24 (OR = 1.2 [0.3–5.2], $p = 0.8373$) [39].

The LIBERTY-CUPID C randomized trial recently evaluated the efficacy and safety of dupilumab as an add-on to sgAHs compared with sgAHs alone in 151 patients with CSU of ≥ 6 years of age who remained symptomatic despite antihistamine use and were omalizumab-naïve. It confirmed the results of CUPID A with 30% of dupilumab-treated patients having complete response at 24 weeks compared with 18% of those on placebo ($p = 0.02$) [40].

Pooled safety data from study A and B were consistent between dupilumab and placebo with treatment-emergent adverse events (TEAE) of 57.3% versus 56.6%, including nasopharyngitis (1.6% versus 5.7%), CSU (8.1% versus 7.4%), and injection-site erythema (2.4% versus 5.7%, Table 4) [39]. In study C, overall rates of TEAE were the same (53%) for both dupilumab and placebo. As compared with placebo, patients treated with dupilumab more commonly experienced (≥ 5%) injection site reactions (12% versus 4%), accidental overdose (7% versus 3%), and COVID-19 infection (8% versus 5%) [40].

The median percent change of total serum IgE concentration decreased during the study period for −48.2% for the dupilumab group versus −6.3% for the placebo group [39]. In CUPID A, dupilumab significantly improved CSU signs

Table 3 Rates of complete response to treatment/complete disease control (UAS7 = 0) and well-controlled CSU (UAS7 ≤ 6) in patients with CSU receiving omalizumab and novel drug treatments; these data are from published randomized controlled trials

Therapy	Study	UAS7 = 0, %		UAS7 ≤ 6, %	
		Placebo	Drug	Placebo	Drug
Omalizumab 300 mg Q4w	Phase 3 ASTERIA I (week 12) [86]***	8.8	35.8	11.3	51.9
	Phase 3 ASTERIA II (week 12) [87]***	5.0	44.0	12.0	66.0
	Phase 3 GLACIAL (week 12) [88]***	4.8	33.7	12.0	52.4
Dupilumab 200–300 mg Q2w	Phase 3 CUPID A (Week 24) [39]***	13.2	31.4	23.5	45.7
	Phase 3 CUPID C (week 24) [40]***	18.0	30.0	–	–
Remibrutinib 25 mg bid	Phase 3 REMIX-1/2 (week 24) [49]	8.2–9.1	28.4–32.1	27.5–35.3	51.9–54.7
Barzolvolimab 150 mg Q4w, 300 mg Q8w	Phase 2 (week 12) [63]	6.4	37.5–51.1*	12.8	59.6–62.5**

UAS7 Weekly Urticaria Activity Score, *bid* twice a day, *Q2w* once every 2 weeks, *Q8w* once every 8 weeks, *Q4w* once every 4 weeks

*Up to 71% at week 52 [63]

**Up to 74% at week 52 [63]

***Biologic-naïve patients

Table 4 Rates of adverse events in patients with CSU receiving omalizumab and novel drug treatments; these data are from published randomized controlled trials

Therapy	Study	AE (serious AE),%		Selected common AEs*	
		Placebo	Drug	Placebo-controlled period, (placebo versus drug), %	Treatment period till week 52, %
Omalizumab 300 mg Q4w	Phase 3 ASTERIA I (week 12) [86]	51.3 (5.0)	56.8 (0.0)	Headache: 2.5 versus 6.2	No data
				Arthralgia: 0.0 versus 3.7	
	Phase 3 ASTERIA II (week 12) [87]	60.8 (3.0)	64.6 (6.0)	Headache: 6.3 versus 10.1	No data
				Arthralgia: 5.1 versus 5.1	
	Phase 3 GLACIAL (week 12) [88]	63.9 (3.6)	65.1 (2.8)	Headache: 3.6 versus 8.7	No data
				Upper respiratory tract infections: 2.4 versus 7.1	
Dupilumab	Phase 3 CUPID A+B [39]	56.6 (5.7)	57.3 (4.0)	CSU: 7.4 versus 8.1	No data
				Nasopharyngitis: 5.7 versus 1.6	
				Erythema at the injection site: 5.7 versus 2.4	
	Phase 3 CUPID C [40]	53.0	53.0	Injection site reactions: 4.0 versus 12.0	No data
				Accidental overdose: 3.0 versus 7.0	
				COVID-19 infection: 5.0 versus 8.0	
Remibrutinib	Phase 3 REMIX-1+2 [49]	64.7 (2.3)	64.9 (3.3)	Respiratory tract infections including COVID-19: 2.0–11.4 versus 3.0–10.7	5.6–15.5
				Headache: 6.2 versus 6.3	7.8
				Urinary tract infection: 2.6 versus 3.1	4.6
				Petechiae: 0.3 versus 3.8	4.0
				Urticaria: 4.9 versus 2.5	3.3
Barzolvolimab	Phase 2 [63]	39 (0.0)	66 (0.0)	Changes in hair color: 0.0 versus 14.0	26.0
				Urticaria: 10.0 versus 10.0	15.0
				Neutropenia / decreased neutrophil count: 0.0 versus 9.0	17.0
				Skin hypopigmentation: 0.0 versus 1.0	13.0
				Nasopharyngitis: 6.0 versus 4.0	10.0

AE adverse events, *Q4w* once every 4 weeks

*≥ 5% for dupilumab, ≥ 3% for remibrutinib and omalizumab, > 10% for barzolvolimab (all dose levels combined); 24 weeks for dupilumab and remibrutinib and 16 weeks for barzolvolimab

and symptoms and reduced serum IgE, regardless of baseline IgE levels [41]. Sustained efficacy of dupilumab seen throughout the off-treatment follow-up period to week 36 points to possible disease-modifying properties [39].

Dupilumab is currently approved for the treatment of several type 2 inflammatory diseases including atopic dermatitis, asthma, and prurigo nodularis [42], and it was recently approved for the use in patients with CSU aged 12 years and older whose disease is not adequately controlled with existing therapy in Japan and the United Arab Emirates (UAE) and is also under regulatory review in the European Union and in the USA.

4 BTK Inhibitors

In CSU, the crosslinking of FcεRI is an important pathway of skin MC activation and their subsequent release of preformed and de novo synthetized inflammatory mediators. Downstream of FcεRI, a network of cytoplasmic signaling proteins including BTK regulates the response of MCs to its activation, where BTK translocates to the cell membrane and phosphorylates downstream targets [43, 44]. This leads to the recruitment of adapter proteins, the activation of calcium channels, and the induction of degranulation of many chemical mediators, including histamines that drive

the development of the signs and symptoms of CSU [45, 46]. In addition, BTK is also present in other immune cells, including basophils, B cells, monocytes, and platelets, and it is involved in other signaling pathways, for example, of the B cell receptor (BCR) and Toll-like receptors (TLRs). Downstream of the activation of the BCR, BTK regulates B cell maturation, differentiation, proliferation, and activation [45]. BTK inhibition rapidly prevents FcεRI-mediated degranulation and de novo cytokine production in MCs [47]. Therapeutic inhibition of BTK has the potential to diminish activation of BCR and TLR signaling pathways and potentially reduce the expansion of B cell populations including autoreactive clonal B cells [45]. In this scenario, BTK inhibitors (BTKi) offer a dual mode of action for treating CSU: they effectively suppress both MC and basophil degranulation, impede the expansion of autoreactive B cells, and reduce levels of MC-activating autoantibodies.

In a phase 2 study with 93 patients with sgAH-refractory CSU, fenebrutinib (GDC-0853), a potent, highly selective, noncovalent, reversible oral BTKi, showed a rapid, dose-dependent improvement in disease activity, including in patients with aiCSU [48]. However, the fenebrutinib CSU program was stopped owing to off-target effects leading to an increase in transaminase in a subset of patients.

The phase 3 CSU development program of remibrutinib (LOU064), an oral, highly selective, covalent, irreversible BTKi, consisted of the twin double-blind, placebo-controlled studies REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157). Studies included 470 (REMIX-1) and 455 (REMIX-2) patients with CSU ≥ 18 years old inadequately controlled by sgAHs. Patients were randomized 2:1 to remibrutinib 25 mg twice-daily or placebo (24 weeks), followed by open-label treatment with remibrutinib (28 weeks). Primary endpoint scenarios were change from baseline in UAS7, ISS7, and HSS7 at week 12. In both of these pivotal studies, primary endpoints were met with superior improvements versus placebo from baseline at week 12 in UAS7 (least squares mean: REMIX-1: − 20.0 versus − 13.8 and REMIX-2: − 19.4 versus − 11.7), ISS7, and HSS7. Patients treated with remibrutinib experienced significant decreases in UAS7, with 46.8–49.8% of patients achieving UAS7 ≤ 6 (placebo: 19.6–24.8%) and 27.9–31.1% reaching UAS7 of 0 (placebo: 6.5–10.5%) at week 12. Similar improvements in UAS7, ISS7, and HSS7 were seen at week 24. Remibrutinib demonstrated a fast onset of action (as early as week 1, as well as at week 24 in patients receiving placebo after transition to remibrutinib) with improvement in disease activity sustained to week 52. At week 52, almost half of the patients showed complete response to treatment with remibrutinib (UAS7 = 0) [49].

Pooled data of REMIX-1 and REMIX -2 trials demonstrated a favorable safety profile of remibrutinib with AEs in the drug group comparable to placebo (all AEs: 64.9% versus 64.7%, serious AEs: 3.3% versus 2.3%, and treatment discontinuation due to AEs: 2.8% versus 2.9%). Exposure-adjusted incidence rates of all AEs did not increase with treatment up to week 52. The most frequent AEs (> 3%) for the entire study period (Table 4) were respiratory tract infections including COVID-19 (5.6–15.5%), headache (7.8%), urinary tract infection (4.6%), petechiae (4.0%), and urticaria (3.3%). Petechiae were more common in the remibrutinib group as compared with placebo during the double-blind treatment period (3.8% versus 0.3%), but were mild or moderate and not linked to clinically significant platelet count decreases. Newly occurring liver transaminase elevations were rare, asymptomatic, and transient/reversible, and they were balanced between remibrutinib and placebo (1.3% versus 1.3%) [49].

In phase 2 and 3 studies, remibrutinib showed similar efficacy in patients with and without features of aiCSU, i.e., basophil histamine release assay positivity, low serum total IgE levels, or those that had prior treatment with omalizumab [50–52]. This is in line with in vitro findings of remibrutinib inhibition of activation of human basophils and MCs induced by the serum of patients with CSU and chronic inducible urticaria (CIndU), regardless of their response to omalizumab [53].

Remibrutinib is currently being investigated in CIndU (NCT05976243) and adolescent patients with CSU (NCT05677451).

Rilzabrutinib, another highly selective, covalent and reversible BTKi that has prolonged BTK occupancy owing to a slow dissociation rate [54], is also under investigation for CSU. A phase 2, 12-week study (RILECSU), followed by a 40-week open-label extension period, included 160 adult patients with moderate-to-severe CSU with insufficient control with sgAHs alone. Patients were randomized to rilzabrutinib 400 mg once every evening, 400 mg twice a day, 400 mg three times a day, or placebo. Rilzabrutinib 1200 mg/day significantly improved ISS7 and UAS7 versus placebo at week 12 (least squares mean: − 9.58 versus − 6.31 and − 17.95 versus − 11.20, respectively). Rilzabrutinib demonstrated a fast decrease in ISS7 score, seen as early as week 1. Rilzabrutinib was well-tolerated, with a higher frequency of headache, nausea, and diarrhea as compared with placebo [55]. Rilzabrutinib decreased median serum levels of IL-31 and soluble Mas-related G protein–coupled receptor X2 (MRGPRX2) as compared with baseline. Efficacy was observed across various prespecified subgroups, i.e., high/low eosinophil levels, high/low baseline IgE levels, and patients with and without history of angioedema. Rilzabrutinib reduced serum levels of IgG anti-TPO and IgG anti-FcεRI, markers of aiCSU [56]. According to the manufacturer, they plan to advance rilzabrutinib into phase 3 development in CSU.

Another orally administered covalent Bruton's tyrosine kinase inhibitor, TAS5315, has been investigated for the treatment of sgAH-refractory CSU in a phase 2a trial (NCT05335499). The primary endpoint was change from baseline in UAS7 at week 12. A total of 126 patients with CSU received TAS5315 (4, 2, 1, 0.5, and 0.25 mg) or placebo once daily for 12 weeks. Clinically significant differences compared with placebo were seen in TAS5315 4 mg, 2 mg, and 0.25 mg groups (4 mg, −8.09, $p = 0.016$; 2 mg, −6.95, $p = 0.034$; 0.25 mg, −8.78, $p = 0.008$). At week 12, complete disease control (UCT score of 16) rates were 29.4% (4 mg), 21.1% (2 mg), 12.5% (1 mg), 5.9% (0.5 mg), 10.5% (0.25 mg), and 5.3% (placebo). All AEs were mild or moderate, with petechiae the most frequently reported treatment-related AE (0–33.3% versus 0% in placebo group) [57, 58].

5 KIT-Targeting Therapies

MCs are key players in the pathogenesis of CSU. MC activation occurs through a complex interplay between signaling pathways, mediator release, and inhibitory receptors [1], leading to a cascade of cellular events including vasodilatation and fluid extravasation, resulting in the clinical manifestation of pruritus, wheals, and angioedema. The KIT receptor and its ligand, stem cell factor (SCF), are both essential in the development and differentiation of MCs from haemopoietic stem and progenitor cells, and in the survival of MCs in the tissue. SCF, the most important MC growth factor, binds to KIT [59], a tyrosine kinase receptor that regulates the growth, differentiation, migration and survival of MC precursors, proliferation and maturation of MC, and regulation of mediator release [60, 61]. KIT is also expressed by cells other than MCs, including hematopoietic stem cells, interstitial cells of Cajal, germ cells, and melanocytes.

Barzolvolimab (previously CDX-0159) is a humanized immunoglobulin G1 kappa (IgG1k) monoclonal antibody that binds to KIT with high affinity and thereby inhibits the binding of SCF. Efficacy of barzolvolimab in treating antihistamine-refractory CSU was demonstrated in a phase 2 trial involving 208 patients (NCT05368285) [62]. Patients were randomized to receive subcutaneous barzolvolimab 75 mg 4-weekly, 150 mg 4-weekly, 300 mg 8-weekly, or placebo during a 16-week placebo-controlled treatment phase, followed by a 36-week active treatment phase, and 24 weeks of follow-up. The study met the primary endpoint of significant improvement in UAS7 versus placebo at week 12 in patients receiving barzolvolimab 150 mg every 4 weeks (least square mean change in UAS7: −23.02 versus −10.47) and 300 mg every 8 weeks (−23.87 versus −10.47). Complete disease control (UAS7 = 0) was seen in 37.5–51.1% of patients with CSU (versus 6.4% in the placebo group), with up to 71% of patients achieving UAS7 of 0 at week 52 (Table 3). UAS7 reduction was observed as early as week 1 and was sustained to week 52. Barzovolimab was effective regardless of prior omalizumab experience [63].

In an open-label trial involving patients with antihistamine refractory cold urticaria or symptomatic dermographism (ClndU, NCT04548869), a single intravenous dose of barzolvolimab (3 mg/kg) [64] led to complete response in virtually all patients, a significant depletion of skin MCs, and decreased tryptase to below the limit of detection. The majority of subjects also demonstrated significant improvement in quality of life measured by the Dermatology Life Quality Index (DLQI).

Barzolvolimab was overall well-tolerated in CSU and CIndU trials, as well as long-term as assessed at week 52 [63]. Most adverse effects were considered to be mild. Most common AEs (> 10%) for the entire treatment period of 52 weeks in the CSU trial were hair color change (26%), urticaria (15%), neutropenia/neutrophil count decrease (17%), skin hypopigmentation (13%), and nasopharyngitis (10%, Table 4). The unique side effect of transient hair color changes (hair whitening) is best explained by effects on KIT-positive hair follicle melanocytes. Similarly, transient effects on taste, observed in some patients, may involve KIT-positive cell populations in taste papillae and taste buds [65]. Reduction of neutrophils was not associated with infections and is expected to be reversible. Data on long-term treatment and follow-up are required to obtain better insight on the safety of blocking KIT.

The phase 3 program, consisting of two phase 3 trials (EMBARQ-CSU1 and EMBARQ-CSU2), will investigate the efficacy and safety of barzolvolimab in adult patients with CSU who remain symptomatic despite sgAH treatment, including patients with prior treatment with biologics.

Briquilimab (previously JSP191, AMG191), an aglycosylated immunoglobulin G1 anti-KIT antibody, is under clinical investigation in the BEACON phase 1b/2a dose escalation study in adult patients with CSU [66].

6 Other Treatments

6.1 JAK Inhibitors

The Janus kinase (JAK) family consists of four types of cytoplasmic tyrosine kinases (JAK1, JAK2, JAK3, and Tyk2) which bind directly to the intracellular domain of cytokine receptors (e.g., IL-4R, IL-5R, IL-6R, and IL-13R) and which can be activated by multiple cytokines. Activated JAKs then phosphorylate STAT proteins, which migrate to the nucleus and upregulate several cytokines, e.g., IL-4, IL-13, IL-31, and TSLP [67, 68].

JAK inhibitors have shown relevant results in many cutaneous diseases such as atopic dermatitis [68]. However, published data for CSU is sparse. Fukunaga and colleagues report the case of a 16-year-old female with primary myelofibrosis and CSU (refractory to antihistamines, corticosteroids, and cyclosporine). Upon starting ruxolitinib for the myelofibrosis, the patient achieved control of the urticaria. However, the authors question whether the urticaria was secondary to the myelofibrosis and whether the response was due to control of the underlying condition [69]. Mansouri et al. reported on four cases of CSU and one of urticarial vasculitis, and Shibu et al. on five cases of CSU, all treated with oral tofacitinib 5 mg twice a day [70, 71]. Patients managed to control their urticaria with tofacitinib, and in some cases achieve remission, despite previous attempts with antihistamines, corticosteroids, cyclosporine and other immunosuppressants. However, none of the patients had tried omalizumab prior to starting tofacitinib.

Data supporting the benefits of JAK inhibitors for CSU are limited to case reports, and side-effect profiles of these drugs should be especially considered (e.g., Herpes zoster and other opportunistic infections, cytopenia, venous thrombosis, and hyperlipidemia) [67]. Currently, there are ongoing or concluded phase 1 trials for TLL018 (NCT05373355) and a phase 2 trial for povorcitinib (NCT05936567) in CSU.

6.2 MRGPRX2 Inhibitors

There are two main pathways for MC activation. The classical IgE-dependent pathway, including cross-linking of the IgE-antigen complex bound to the high-affinity IgE receptor FcεRI. Alternatively, there are IgE-independent pathways, and different receptors have been associated with these pathways [72]. The Mas-related G protein–coupled receptor X2 (MRGPRX2) is a novel G protein–coupled receptor and one of four in the MRGPRX family (MRGPRX1-X4) [72, 73]. In humans, besides the dorsal root ganglia, connective tissue MCs are the only cells that express the MRGPRX2 [72, 74].

Many observations have made MRGPRX2 a target of interest in CSU. First, MRGPRX2 (and its mouse ortholog, mrgprb2) knockout in human and mouse MCs resulted in a significant abolishment of MC degranulation and of allergic reactions [73]. Second, in patients with CSU there is a higher percentage of MRGPRX2-positive MCs compared with healthy subjects, even though there is a similar number of MCs in the lesions [75]. Third, intradermal injection of different MRGPRX2 ligands (substance P, vasoactive intestinal peptide, atracurium, and icatibant) generated greater wheal responses in patients with CSU in comparison with healthy subjects, with wheal responses similar to that of histamine [76, 77]. In addition, in CSU there is eosinophil infiltration of the wheals and prominent deposition of the major basic protein and eosinophil cationic protein, both of which can activate MRGPRX2 and degranulate MCs [72]. Finally, in vitro data showed that coactivation of IgE and MRGPRX2 can lead to a more pronounced MC activation with an additive effect [78].

The extent to which these and other non-FcεRI mediated mechanisms are responsible for MC degranulation in CSU has not yet been conclusively determined. Nonetheless, given the importance of this receptor, MRGPRX2 inhibitors are very promising therapeutic drugs in a variety of MC-mediated diseases [72].

MRGPRX2-targeted treatments can be divided into three categories: (1) direct inhibition of MRGPRX2, (2) inhibition of MRGPRX2 downstream signaling (for example by suppressing the elevation of intracellular calcium), and (3) other mechanisms such as the activation of CD300f, a known suppressor of MRGPRX2-mediated MC activation [72]. This is still a novel area of research; mechanistic studies and clinical trials with MRGPRX2 inhibitors are a promising field for MC-mediated diseases. Currently, there are ongoing phase 1B (NCT06050928) and phase 2 (NCT06077773) trials for EP262 in CSU and a phase 1 trial for EVO756 in CSU.

7 Conclusions and Outlook

The drug pipeline in CSU is developing rapidly, with omalizumab biosimilars entering the market and novel small molecules and biologics becoming available in the next 1–2 years. CT-P39 (Omlyclo®) is the first omalizumab biosimilar in Europe recently approved by the European Commission. Dupilumab and remibrutinib may be soon approved for antihistamine-unresponsive CSU worldwide and may also help patients without sufficient response to anti-IgE therapies and those with comorbidities.

Endotyping patients with CSU—such as differentiating between autoimmune, autoallergic, overlapping, or non-FcεRI receptor mediated forms—along with identifying specific biomarkers such as total IgE [79] and basophil tests will enable tailored treatments in the context of precision medicine, optimizing therapeutic efficacy. Some treatments such as BTKi and anti-KIT have potential to benefit difficult-to-treat CSU endotypes such as aiCSU.

There are a number of novel anti-IgE approaches in various development phases, e.g., YH35324; IgE_{Trap}-Fc protein (phase 1: NCT05960708); LP-003, a novel high-affinity, long-acting anti-IgE antibody (phase 2: NCT06228560); and an IgE-neutralizing UB-221 monoclonal antibody with superior IgE-neutralizing activity to that of omalizumab (phase 2: NCT05298215) (reviewed elsewhere [80]). Several novel drugs are in preclinical development and phase I CSU studies, including an oral small molecule KIT inhibitor, MOD000001 [81]; a monoclonal antibody activating inhibitory MC-receptor

Siglec-6, AK006; and an C4aR1 inhibitor, INF904 (Table 2). In the long term, more MC-specific approaches may further improve urticaria management. They include targeting several cytokine pathways or CSU drivers simultaneously (e.g., bispecific or trispecific antibodies [82] or combination therapies, e.g., with omalizumab and dupilumab), targeting gut microbiome alterations [83], and vaccine therapies, such as against IgE, IL-4, and/or IL-13 [84].

Finally, future studies with long-term follow-up will show whether any of the novel treatments, e.g., BTKi and dupilumab [39, 85], possess disease-modifying properties and will be game-changers in CSU management.

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Declarations

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