From Research to Practice: The Latest Data on Evolving Treatments for Chronic Spontaneous Urticaria

Based on a Medscape Education Online Activity

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Target Audience

This activity is intended for dermatologists, allergists and clinical immunologists, primary care providers, physician assistants, nurse practitioners, nurses, and pharmacists.

Goal Statement

The goal of this activity is for learners to be better able to assess disease burden and emerging treatments for chronic spontaneous urticaria (CSU), including their safety and efficacy data.

Learning Objectives

Upon completion of this activity, participants will:

Have increased knowledge regarding the

- Burden and unmet needs in managing CSU
- Clinical data for new and emerging CSU therapies

Have greater competence related to

- Individualizing treatment strategies for patients with CSU

Demonstrate greater confidence in their ability to

- Incorporate new treatment strategies into practice

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From Research to Practice: The Latest Data on Evolving Treatments for Chronic Spontaneous Urticaria

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ABSTRACT

Chronic spontaneous urticaria (CSU) should be on every dermatology practitioner's radar. CSU is a skin disorder marked by wheals, angioedema, or both for more than 6 weeks. Patients with CSU experience unexplained, itchy wheals that appear and disappear, traveling around the body and lasting less than 24 hours per area. Angioedema accompanies wheals for up to 48 hours in around half of cases. CSU is a diagnosis of exclusion, relying heavily on patient history to differentiate CSU symptoms from other causes of urticaria or angioedema. But reassuringly, CSU has a simple diagnostic algorithm and a clear initial treatment path. First-line strategies include non-pharmacologic approaches, and second-generation antihistamines (2gAH) administered up to 4 times their standard dose. Omalizumab and cyclosporine (off-label) are second- and third-line options, respectively. However, many patients will continue to have CSU symptoms despite consistent maximum-dose treatment. Novel therapies, including biologic agents and small molecule drugs targeting mast cell activation and inflammatory mediators, show promise in treating CSU refractory to standard therapy. However, further research is needed to establish their efficacy and safety in clinical practice.

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Chronic spontaneous urticaria (CSU) is defined as the spontaneous appearance of wheals, angioedema, or both for more than 6 weeks.[1,2] Unlike chronic inducible urticaria, CSU symptoms cannot be induced through provocation tests and are independent of environmental conditions and allergens. Visually, symptoms cannot be distinguished from other causes of urticaria or angioedema, making a detailed patient history crucial for diagnosis.

Signs and Symptoms

Patients with CSU will experience unexplained, pruritic hives called wheals. These wheals typically appear for less than 24 hours in one area before fading and reappearing in a different area of the body. Episodes of wheals appearing sporadically and seemingly at random can persist for several days.[1] The associated pruritus can be severe and even disabling, leading some to refer to the condition as "the devil's itch."[3] Though wheals present more frequently, 43% to 59% of patients will also experience angioedema.[4] This swelling can last up to 48 hours. Roughly 10% of patients with CSU present with angioedema as their primary symptom.[3]

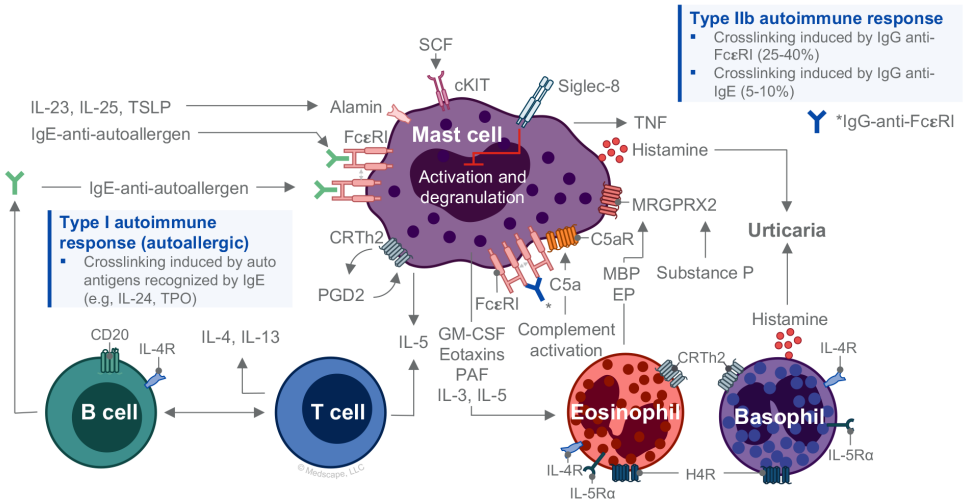
Pathophysiology

CSU is primarily mediated by dermal mast cells.[5] These mast cells degranulate, triggering histamine-facilitated vasodilation and increased vascular permeability that manifests clinically as pruritic wheals or angioedema.[5] The exact mechanism triggering this initial mast cell degranulation remains unclear.[5] Three subtypes of CSU exist: type I (autoallergic, immunoglobulin [Ig]E mediated), type IIb (autoimmune, IgG autoantibody-mediated), and cause unknown.[4,6] Type IIb is believed to cause higher disease activity than type I, but the utility of these subtypes in predicting treatment response or symptom burden is unclear (Figure 1).[4]

Burden of CSU Disease in the United States

An estimated 500,000 people suffer from chronic urticaria of any etiology, but the true figure is likely higher.[7] When CSU

FIGURE 1. Pathophysiology of type I and type IIb CSU.[5]



Adapted from Kaplan A, Lebwohl M, Giménez-Arnau AM, et al. Chronic spontaneous urticaria: focus on pathophysiology to unlock treatment advances. *Allergy.* 2023;78:389-401.

symptoms first appear, patients often think they're having an allergic reaction, leading to an average 2-year duration between symptom onset and CSU diagnosis.[8] And even when diagnosed, the majority of patients remain untreated or undertreated.[9,10] The unpredictable nature of CSU symptoms creates substantial frustration and anxiety for patients, and mental health challenges and emotional distress are common.[11] Patients also suffer indirect financial strain due to work absenteeism for severe outbreaks or medical appointments, with an average of 15.1 office visits per year.[12]

Comorbidities

Patients with CSU may be more likely to have autoimmune comorbidities, including autoimmune thyroid conditions. Thyroid autoantibodies are relatively common, resulting in higher rates of thyroid dysfunction in people with CSU than in the general population. Appropriate management of thyroid conditions has been associated with decreased CSU symptom burden.[13]

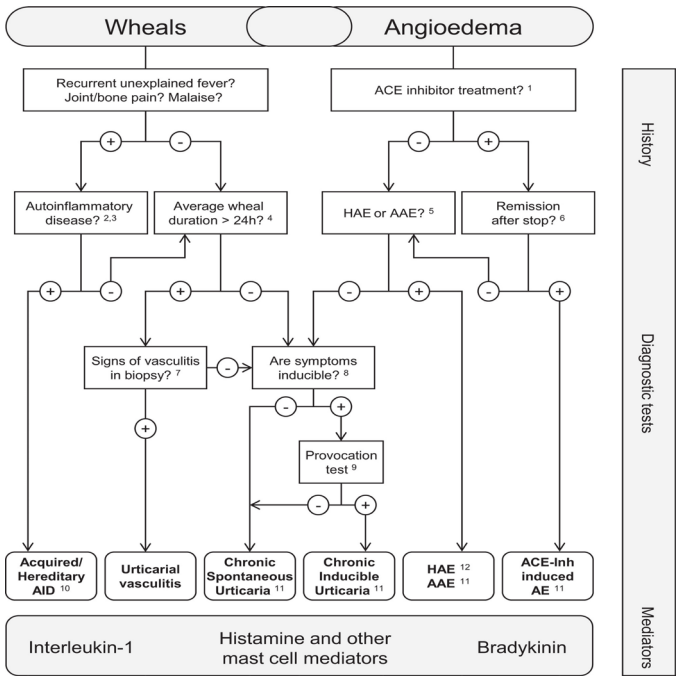
CSU Diagnosis in the Clinical Setting

The guidelines for urticaria are somewhat unusual in that a large international group came together and reached a consensus on best practices.[1] The International European Academy of Allergology and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF; EuroGuiDerm EAACI/GA²LEN/EurioGuiDerm/Asia Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI) guideline is the most thorough source of information available for questions pertaining to the identification, diagnosis, and management of CSU and other forms of urticaria.

A Diagnosis of Exclusion

CSU diagnosis involves using a detailed patient history and limited diagnostic testing (Figure 2).[1] Fundamentally, CSU is diagnosed by ruling out other causes of urticaria or, if present,

FIGURE 2. Urticaria diagnostic algorithm from 2022.[1]



HAE, hereditary angioedema; AAE, acquired angioedema.
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angioedema. The timing of symptoms is also a crucial aspect of diagnosis: wheals must last 24 hours or less and occur intermittently for 6 or more weeks.

Anamnesis

The spontaneous nature of CSU symptoms complicates diagnosis. The patient may make an appointment while experiencing severe, disruptive symptoms. But they may have no wheals on the day of their appointment. As a result, practitioners must rely heavily on patient memory. Photography is extremely helpful for this condition, and patients should be encouraged to document their symptoms. For example, if patients bring photographs of wheals that were present 48 hours ago and are now absent, urticarial vasculitis can generally be ruled out without the need for a biopsy.[14]

Workup

The international guidelines recommend restraint during the workup for CSU due to the associated costs and the limited benefit of ordering numerous tests.[1] Casting a wide net of blood panels and allergy tests risks catching a red herring: for example, lab work may reveal a nickel allergy having nothing to do with the patient's CSU symptoms. Practitioners can prevent patients' unnecessary stress, time, and financial expenditure by emphasizing that CSU is an autoimmune condition that can be managed without additional testing.

A Team-Based Approach to CSU

Once differential diagnoses are ruled out and criteria are met for CSU, the entire care team must understand and convey that the patient is experiencing an autoimmune issue rather than an allergy.[14] Whole-person care is also essential for patients with CSU in any setting, as CSU can have wide-ranging impacts on patient psychosocial well-being.[14] Initial treatment consists of a second-generation antihistamine (2gAH) at the standard dose and up to 4 times the standard dose (off-label) before progression to more advanced therapy.[1] If a patient is responding to antihistamines and does not require advanced therapy, CSU can be managed by a dermatologist, an allergist, and, in some situations, primary care.

Subspecialty Care

For patients who do not have a primary care provider who can manage care or who require subspecialty attention for diagnosis and management, the choice between a dermatologist and an allergist can depend on access. Both specialists play similar roles in CSU management, but some cities or rural areas may not have an allergist or might have long wait times for a dermatologist.[15,16]

Dermatology

When patients present to dermatology, they stand to benefit from specialized management. Dermatologists may be more experienced at applying diagnostic tests to rule out other causes of urticaria, such as temperature or pressure challenges for induced urticaria. Being under the care of a dermatologist may be especially beneficial for patients whose symptoms do not respond to treatment. Dermatologists may be more well-equipped than primary care to use scoring thresholds for step-up or step-down care since these types of tools are common in everyday practice.[17]

A Deep Dive into CSU Treatment

Non-Pharmacologic Approaches

For CSU, non-pharmacologic strategies include identifying and eliminating underlying triggers (eg, inflammatory and infectious processes) with the aim to cure the disease. Additionally, managing comorbid conditions, such as chronic inducible urticaria, by avoiding physical triggers (eg, heat, cold, pressure, stress) and certain drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) can help diminish CSU activity.[1]

Disease Severity Assessment

The urticaria activity score (UAS) can be used to monitor disease activity (Table 1). The UAS7, which is the UAS administered for 7 days, is the most common patient-reported outcome (PRO) in clinical practice.[1] Treatment goals are a UAS7 score of 0, with complete control and normalization of quality of life (QoL). Pharmacologic agents for CSU should be used until signs and symptoms of the disease disappear.[1] For patients with angioedema, the angioedema activity score (AAS) can be used

TABLE 1.

UAS for Assessment of CSU Disease Activity[1]		
Score	**Wheals**	**Pruritus**
0	None	None
1	Mild (< 20 wheals/24 hours)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 hours)	Moderate (troublesome but does not interfere with normal daily activities or sleep)
3	Intense (> 50 wheals/24 hours or large confluent areas of wheals)	Intense (severe pruritus that interferes with normal daily activities or sleep)

to assess and monitor disease activity.[1] Other metrics, including the itch severity score (ISS7) and urticaria control test (UCT), are used in clinical trials.[4]

First-Line Pharmacologic Approach

Urticaria is considered a mast-cell-driven disease, and traditional treatments target mast cell mediators and activators such as histamine and autoantibodies. There are still some misconceptions among general practitioners who, following old guidelines, prescribe an H1 antihistamine and then add an H2 antihistamine. H2 antihistamines provide no treatment benefit for CSU.[18] Further emphasis on educating practitioners about the type of H1 antihistamine is also needed: First-generation H1 antihistamines (1gAH), such as diphenhydramine and hydroxyzine, cause drowsiness and have several drug interactions; 2gAH agents are now the preferred first-line therapy.[1] The 2gAH drug class includes bilastine, cetirizine, desloratadine, ebastine, fexofenadine, and levocetirizine. These drugs may be administered up to 4 times the maximum licensed dose, but it should be kept in mind that uptitration is considered an off-label practice.[1,19,20] Since no strong head-to-head trials exist comparing the relative efficacy of these agents in CSU, specific recommendations prioritizing the use of each antihistamine drug cannot be made at this point.

Second- and Third-Line Pharmacologic Approaches

Therapeutically, few options are available to treat CSU that is refractory to 2gAHs. CSU refractory to antihistamines can be treated with omalizumab, which is approved by the US Food and Drug Administration (FDA) for use in CSU, in combination with a 2gAH.[21,22] The omalizumab dose may be increased off-label and/or the dosing interval shortened, if initial treatment is ineffective.[1,20]

Cyclosporine (off-label) in combination with 2gAH may be considered as third-line therapy if omalizumab and 2gAH fail.[1,23] Patients taking cyclosporine should be monitored for nephrotoxicity and hypertension and the dose adjusted accordingly.[24,25] Notably, cyclosporine is considered safer for use in CSU than long-term steroids; however, short courses of glucocorticoids may be used for acute exacerbations.[1,20] Available options for CSU leave many patients without relief, highlighting the need for safer, more effective treatments capable of altering the disease course and quelling symptoms.[1,19,26,27]

Novel Biomarker Development

Though reasons for treatment nonresponse remain unclear, some biomarkers have been associated with response or nonresponse to available agents. High disease activity, d-dimer levels, and C-reactive protein levels are good predictors of nonresponse to 2gAH treatment. Low total IgE levels are predictive of poor response to omalizumab. Positive response to cyclosporine treatment can be predicted by positive basophil histamine release assay. Though promising, these biomarkers require additional investigation as tools for use in clinical practice.[28]

New and Emerging Pharmacologic Agents for the Management of CSU

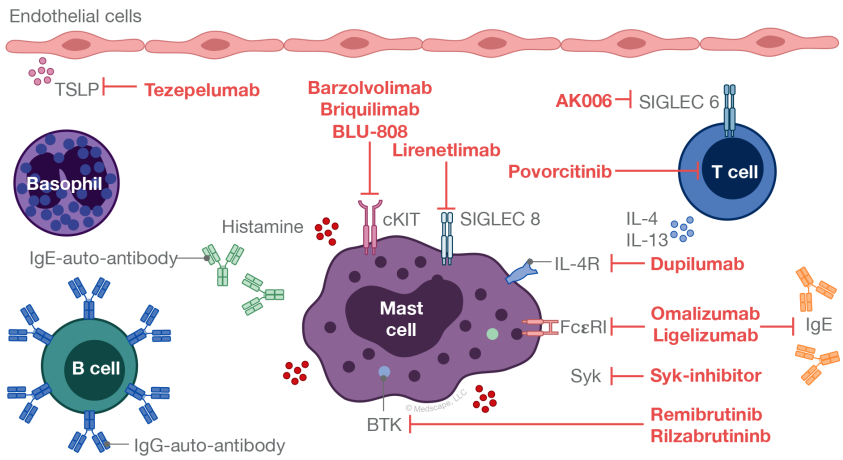
Drugs under clinical investigation for CSU target mast cell activation and inflammatory mediators thought to be involved in the development of CSU (Figure 3).[19,27,29] Trial details and key endpoints are summarized in Table 2.

Biologic Agents

Dupilumab

Blockade of Th2 cytokines, including interleukin (IL)-4, IL-5, and

FIGURE 3. New and emerging targeted therapies for the management of CSU.[19,28,29]



Adapted from Melchers S, Nicolay JP. Chronic spontaneous urticaria—status quo and future. *Allergo J Int.* 2023;32:326-336.

IL-13 reduces IgE production, limiting mast cell and basophil activation in CSU. Dupilumab, an anti-IL-4/13Ralpha-targeting monoclonal antibody is used off-label for treating CSU.[19,27,29] The phase 3 randomized LIBERTY-CSU CUPID study A (N = 138) demonstrated significant improvement in urticaria activity and itch severity with dupilumab added to standard dose antihistamine compared to antihistamines alone (difference vs placebo, -8.5 [95% CI, -13.2, -3.9; *P*=0.0003] for UAS7 and -4.2 [95% CI, -6.6, -1.8; *P*=0.0005] for ISS7).[30] Similar proportions of treatment-emergent adverse events (AEs) occurred in both groups; the most common were nasopharyngitis and injection-site erythema.

In the LIBERTY-CSU CUPID study B, patients (N = 108) remaining symptomatic despite H1 antihistamines who were incomplete responders or intolerant to omalizumab showed improvements in UAS7 scores (difference: -5.8 [95% CI: -11.4, -0.3; *P*=0.0390]) with dupilumab vs placebo. A trend toward improvement in ISS7 scores was also noted (difference: -2.9 [95% CI: -5.7, -0.07; nominal *P*=0.0449, not significant]).[30] Although the primary endpoint was not achieved, a small effect of dupilumab was observed among patients who were omalizumab-intolerant/incomplete responders.[30] The FDA has requested additional efficacy data to support dupilumab's indication in CSU. The publication of LIBERTY-CUPID study C results may provide these needed data.[31-34]

Barzolvolimab

The KIT receptor and its ligand are critical regulators of mast cell differentiation, maturation, and survival. Barzolvolimab is an anti-KIT monoclonal antibody shown to be effective in managing CSU.[19,27] Recent phase 1 data showed dose-dependent improvements with barzolvolimab in disease activity measures among patients with CSU (N = 45), including UCT improvement and tryptase level suppression.[35] By week 8, dose-dependent reductions in UAS7 were observed across 3 barzolvolimab doses (0.5 mg/kg, -15.8 [standard error of the mean, 3.33], 1.5 mg/kg, -19.6 [4.73], and 3 mg/kg, -22.7 [3.92] vs placebo, -12.4 [5.549]). Common AEs reported in 10% or less of barzolvolimab-treated patients included urinary tract infections, headache, neutropenia, and back pain.[35] A phase 2 study is ongoing in patients (N = 208) with CSU refractory to antihistamines, with preliminary results showing significant improvement in UAS7 at week 12 (difference in the least square mean [LSM] change from baseline to week 12 vs placebo, -12.55, *P*<0.0001 for 150 mg and -13.41, *P*<0.0001 for 300 mg). Most AEs were low-grade with no serious drug-related AEs reported.[36,37]

Small Molecule Drugs

Remibrutinib

As a potent oral inhibitor of Bruton tyrosine kinase (BTK), remibrutinib reduces mast cell degradation and IgG/IgE production in CSU.[19,27] A phase 2 trial (N = 311) has demonstrated significant symptom improvement and reduced urticaria activity (weekly UAS change at week 4: -19.1 [10 mg once daily], -16.0 [10 mg twice daily], -20.0 [25 mg twice daily], -19.1 [35 mg once daily], -14.7 [100 mg once daily], -18.1 [100 mg twice daily] vs -5.4 for placebo; nominal *P*<0.0001 for all doses vs placebo).[38] Most associated AEs with remibrutinib were mild or moderate (ie, infections and skin manifestations).[38] In a separate phase 2 trial (N = 309), all remibrutinib doses improved the QoL of patients with CSU up to week 12 compared to placebo.[39]

Rilzabrutinib

In a phase 2 study, rilzabrutinib, another BTK inhibitor, showed a significant reduction at week 12 in ISS7 scores (LSM, -9.58 vs -6.31 with placebo; *P*=0.0181) and UAS7 scores (LSM, -17.95 vs -11.20 with placebo; *P*=0.0116) in patients with mild to moderate CSU.[40] Some AEs, including headache, nausea, and diarrhea, were more frequent with rilzabrutinib than placebo.[40]

Other Novel Therapies

Additional biologic agents reaching various stages of clinical development include ligelizumab, a humanized anti-IgE monoclonal antibody; lirentelimab, an anti-sialic acid-binding, immunoglobulin-like lectin (SIGLEC-8) monoclonal antibody; and tezepelumab, an anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody.[19,27,29] However, recent phase 2 data for lirentelimab and tezepelumab have not been positive, with trials either being terminated or failing to meet key primary endpoints.[41-44] Additionally, phase 3 studies of ligelizumab failed to show superior efficacy over omalizumab for patients with moderate to severe H1 antihistamine-refractory CSU.[29,45,46] Other biologic agents are in early phases of development, including AK006, a monoclonal antibody targeting SIGLEC-6, which inhibits IgE-mediated activation and degranulation, and briquilimab, an anti-KIT antibody, which blocks stem cell factor signaling and regulates mast cell function.[47-49]

Studies are ongoing for the small molecule inhibitors, povorcitinib, a Janus kinase 1 inhibitor in phase 2 of development, and BLU-808, a wild-type c-KIT inhibitor in preclinical studies. Trial results have not yet been published.[47,50-52] Trials investigating novel treatments for CSU are summarized in Table 2.

TABLE 2.

Novel Agents Investigated for the Management of CSU

Drug	Trial Information	Key Endpoint(s)/ Measurements	Trial Status
Tezepelumab[41]	NCT04833855, INCEPTION, Phase 2 (N = 125)	Primary endpoint: Change from baseline at week 16 in UAS7	Completed; primary endpoint not met, but showed significant improvement in UAS7 with 210 mg dose; *P*= 0.037 vs placebo and 420 mg dose, *P*=0.062 vs placebo
Lirentelimab[42-43]	Phase 2 (N = 45)	Primary endpoint: Change in UCT score at week 22	Mean changes at week 22 of 11.1 ± 4.1 (cohort 1), 4.8 ± 7.0 (cohort 2), 6.5 ± 6.2 (cohort 3), and 3.4 ± 4.1 (cohort 4) and complete response rates (UCT score ≥ 12) of 92% (cohort 1), 36% (cohort 2), 82% (cohort 3), and 40% (cohort 4), respectively*
		Key secondary endpoint: Change from baseline at week 22 in UAS7	Completed; omalizumab-naive and omalizumab-refractory patients (mean UAS7 change, -73% and -47%, respectively); achieved UAS7 response rates (≥ 50% reduction) 77% and 45%, respectively
	NCT05528861, MAVERICK, Phase 2 (N = 127)	Primary endpoint: Absolute change from baseline at week 12 in UAS7	Completed; no further trials planned (failed to meet the primary endpoint)
Ligelizumab[44-46]	NCT03580369, PEARL 1, Phase 3 NCT03580356, PEARL 2, Phase 3 (N = 2057 for both trials)	Primary endpoint: Change from baseline at week 12 in UAS7	Completed; ligelizumab (120 mg and 300 mg) superior vs placebo, but not omalizumab in both studies (*P*<0.0001)
	NCT04210843, Phase 3 (N = 1033)	Primary endpoint: Percentage of subjects receiving the same dose regimen as in the core studies (NCT03580369, NCT03580356), with well-controlled disease (UAS7 ≤ 6) at week 12	Terminated (not due to safety concerns)
AK006[47,48]	NCT06072157, Phase 1 (N = 140)	Primary endpoints: Incidence and severity of AEs, the incidence of AEs of special interest, and AEs leading to discontinuation	Results not yet available
Briquilimab[49]	Preclinical	Mouse model: passive systemic anaphylaxis sensitization assays and core body temperature analysis	Protected mice from anaphylactic reactions on passive systemic anaphylaxis core body temperature of 36.8 ± 1.0°C similar to 37.8 ± 0.8°C in control animals [*P*=0.440]) and decreased mast cell numbers
BLU-808[50]	Preclinical study	Human-derived mast cell assays: cell proliferation and c-KIT phosphorylation	Potently inhibited mast cell degranulation
		Rodent models	Oral rodent models showed robust inhibition of histamine release after challenge with stem cell factor
Povorcitinib[51,52]	NCT05936567, Phase 2 (N = 136)	Primary endpoint: Change from baseline at week 12 in UAS7 score	Results not yet available

*Patients in this study were separated into the following 4 cohorts: n = 13, omalizumab-naive CSU; n = 11, omalizumab-refractory CSU; n = 11, cholinergic urticaria; n = 10, symptomatic dermographism.

Chronic Spontaneous Urticaria: A Case in Context

This fictionalized case is intended to represent common clinical signs rather than a specific patient.

Presentation: A 36-year-old male patient presents to a dermatology clinic reporting intermittent pruritic wheals that first started appearing approximately 10 weeks prior to the visit. Once the wheals develop, they can occur anywhere on his body and tend to be gone within a day before appearing in a different location. They do not correlate with changes in his diet, medications, or environment. The patient reports that when he experiences a flare, the itching impacts his sleep, concentration, and mood. He is not experiencing any other symptoms but emphasizes the disruptive nature of the wheals and pruritus in his occupation as a long-haul truck driver.

He reports taking over-the-counter diphenhydramine (25 mg) every 4 to 6 hours during flares to control the itching, but he is concerned that the agent does not work well. While the treatment helps him sleep at night, he experiences significant daytime drowsiness, and he worries about the impact on his employment as a trucker. The patient asks for testing to assess the source of his allergies and requests that the dermatologist biopsy his skin and administer allergy testing to ascertain the root cause of the symptoms.

Actions: After hearing the patient's history and assessing currently present wheals and photos of previous lesions, the dermatologist reassures the patient that no additional testing is needed because the nature and duration of the patient's symptoms fall within diagnostic guidelines for CSU.

Outcome: The patient is diagnosed with CSU and instructed to take loratadine once daily for two weeks, regardless of the presence of wheals, and advised that he can increase to 2 to 4 tabs once daily if he continues to get new lesions. He will return in 4 to 6 weeks for follow-up.

Diagnosis

Patients often experience substantial diagnostic delays due to the remitting nature of the symptoms and apparent similarity to other conditions, resulting in waits of 2 years on average from onset to diagnosis and treatment initiation.[53] Diagnosis of CSU involves exclusion of signs and symptoms of other causes of wheals or angioedema; for example, CSU wheals are not associated with pain (unlike autoinflammatory disease), tend to last less than 24 hours (unlike urticarial vasculitis), and are not inducible (unlike chronic inducible urticaria).[1] Angioedema symptoms can lead to a CSU diagnosis through similar exclusionary logic.[1]

Diagnostic Misconceptions

The lack of diagnostic certainty is a source of confusion and misconceptions for many clinicians and may lead to unnecessary biopsies, allergy tests, and referrals. Some clinicians administer testing to reassure patients that their concerns are being heard and understood. However, these laboratory workups are clinically unnecessary in most cases and can result in unwarranted costs and use of resources.[14]

Treatment Initiation

The international guidelines for urticaria, which have been endorsed by the American Academy of Dermatology along with over 50 other organizations, recommend 2gAH agents as the first-line treatment for new-onset CSU.[1] First-generation H1 antihistamines, such as diphenhydramine and dimenhydrinate, cross the blood-brain barrier and cause sedation, loss of coordination, and impairment of cognitive function. More troublingly, 1gAHs may be associated with an increased risk of dementia in older patients.[54] While 2gAHs also cross the blood-brain barrier, they accumulate in much lower concentration in the central nervous system, resulting in minimal to nonexistent sedative or cognitive impacts.[54,55]

2gAH Selection and Dosage

Current international guidelines make no recommendation for the use of one 2gAH agent over another for the treatment of CSU. Treatment initiation should begin at the standard dosage for each agent, but good evidence exists for off-label uptitration to as much as 4 times the standard dosage in patients with uncontrolled or incompletely controlled disease activity.[20,56,57] Increasing 2gAH dosage is preferred over the addition of a second agent or an immune modulator.[1,20]

Follow-up: Patient returns with nonresponse to standard (1-time daily) loratadine treatment

Presentation: The patient returns to a dermatology clinic after 4 weeks to follow up after diagnosis with CSU and initiation of loratadine treatment. After 2 weeks, he had increased his loratadine to 2 times daily. He reports that although his daytime drowsiness has subsided since cessation of diphenhydramine treatment, he still struggles to sleep due to persistent itching. He does not believe the treatment is working.

Outcome: The patient is instructed to take loratadine 3 times daily. After a follow-up telehealth visit 2 weeks later in which the patient reports an ongoing lack of treatment efficacy, the dosage is increased to 4 times daily.

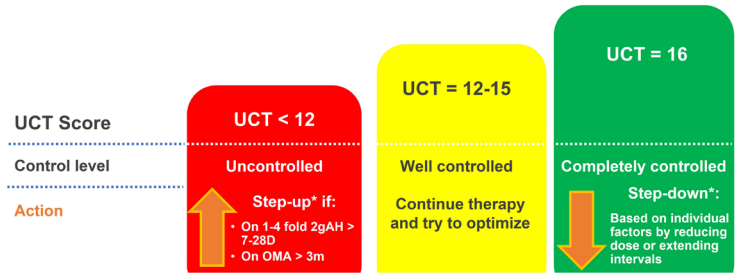
Step-Up Treatment

Some patients require increased 2gAH dosage to achieve symptomatic control: In fact, almost 60% of patients with CSU will have inadequate clinical response to standard-dose 2gAH treatment.[20] When increasing dosage, 2 to 4 weeks should generally be allowed for assessment of treatment response before additional adjustments are made to the treatment regimen.[20] The majority of patients (63.2%) who do not respond to standard-dose 2gAHs will respond to increased dosages, though the responders generally experience reductions in pruritic symptoms rather than decreased wheal frequency.[56]

Assessing Treatment Efficacy

In practice, clinicians may find qualitative PROs of pruritus, swelling, and hives sufficient to assess changes in disease activity. However, clinicians seeking a quantitative metric may direct patients to self-administer the UAS7 tool for disease activity (Table 1) or the UCT for disease control. Quantitative metrics may be useful in deciding whether to step up or step down treatment and in comparing disease activity measures from different clinical practices (Figure 4).[4]

FIGURE 4. Suggested thresholds for treatment step-up and step-down in patients with urticaria.[1]



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Follow-up: Patient returns with treatment nonresponse to 4-times-daily loratadine

Presentation: The patient returns to the clinic reporting no improvement in the frequency or duration of his pruritic wheals even with a maximum 2gAH administration frequency for 4 weeks. He reports small improvements in the degree of itching but emphasizes that the symptoms remain disruptive to his daily life.

Outcome: The dermatologist suggests adding omalizumab. After educating the patient on the risk of anaphylaxis and obtaining consent, the dermatologist administers the subcutaneous injection (150 mg) at the appointment. The patient schedules a return appointment for his next injection in 4 weeks.

Treatment Nonresponse With 2gAH

In many cases (> 50%), patients will experience CSU symptoms that do not respond to or remain uncontrolled despite consistent maximum-dose 2gAH treatment.[11] Patients who are refractory to treatment commonly use more healthcare resources, undergo more testing, and may suffer from a greater number of comorbidities. However, the factors associated with nonresponse to antihistamine therapy remain unclear.[26]

Omalizumab

The only FDA-approved, on-label option for these patients is omalizumab.[1] International guidelines recommend omalizumab as an add-on to 2gAH treatment in patients whose symptoms remain uncontrolled. Some clinicians may be hesitant to administer omalizumab due to reports of anaphylactic reactions in premarket clinical trials and in clinical practice. However, these reactions are rare, occurring in less than 0.1% of cases, and most anaphylactic reactions (60% to 70%) occur within the first 3 doses.[23] Rural clinics lacking proximate access to emergency care may consider referral to an allergist. However, referral to allergy specialists is not always necessary given the rarity of life-threatening reactions.

Inadequate Omalizumab Response

Nearly one-third of patients on omalizumab therapy (150 mg or 300 mg) have uncontrolled disease after 6 months of treatment.[58] At that point, international guidelines recommend the addition of cyclosporine, which has immunosuppressive effects.[1] Some real-world data support the safety and efficacy of up-dosing omalizumab beyond the licensed 150 mg or 300 mg treatments, although no controlled trials have been conducted.[58]

Emerging Therapies

If available treatments are ineffective, there are some other options under development or treatments for other disease states that have some evidence of efficacy with off-label usage.[19] Some authors suggest off-label usage of other immune modulators or immunosuppressants for the treatment of CSU.

Treatment Cessation

In patients with good responses to treatment, clinicians may struggle to ascertain the best strategy and timing for treatment tapering or cessation. CSU remission, like CSU onset, is spontaneous and difficult to predict. Antihistamines can be tapered and stopped after 3 months of complete control, and omalizumab treatment can conclude after 6 to 12 months of complete control.[2]

DISCLOSURES

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REFERENCES

1. Zuberbier T, Latiff AHA, Abuzakouk M, et al. The international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy.* 2022;77:734-766.
2. Terhorst-Molawi D, Fox L, Siebenhaar F, et al. Stepping down treatment in chronic spontaneous urticaria: what we know and what we don't know. *Am J Clin Dermatol.* 2023;24:397-404.
3. Saini SS, Kaplan AP. Chronic spontaneous urticaria: the devil's itch. *J Allergy Clin Immunol Pract.* 2018;6:1097-1106.
4. Armstrong AW, Soong W, Bernstein JA. Chronic spontaneous urticaria: how to measure it and the need to define treatment success. *Dermatol Ther.* 2023;13:1629-1646.
5. Kaplan A, Lebwohl M, Giménez-Arnau AM, et al. Chronic spontaneous urticaria: focus on pathophysiology to unlock treatment advances. *Allergy.* 2023;78:389-401.
6. Kolkhir P, Church MK, Weller K, et al. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immun.* 2017;139:1772-1781.e1.
7. Wertenteil S, Strunk A, Garg A. Prevalence estimates for chronic urticaria in the United States: a sex- and age-adjusted population analysis. *J Am Acad Dermatol.* 2019;81:152-156.
8. Maurer M, Abuzakouk M, Bérard F, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy.* 2017;72:2005-2016.
9. Wagner N, Zink A, Hell K, et al. Patients with chronic urticaria remain largely undertreated: results from the DERMLINE online survey. *Dermatol Ther.* 2021;11:1027-1039.
10. Maurer M, Abuzakouk M, Bérard F, et al. Antihistamine-resistant chronic spontaneous urticaria remains undertreated: 2-year data from the AWARE study. *Clin Exp Allergy.* 2020;50:1166-1175.
11. Staubach P, Dechene M, Metz M, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol.* 2011;91:557-561.
12. Broder MS, Raimundo K, Antonova E, et al. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. *Am J Clin Dermatol.* 2015;16:313-321.
13. Kolkhir P, Metz M, Altrichter S, et al. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. *Allergy.* 2017;72:1440-1460.
14. Metz M, Altrichter S, Buttgereit T, et al. The diagnostic workup in chronic spontaneous urticaria–what to test and why. *J Allergy Clin Immunol Pract.* 2021;9:2274-2283.
15. Feng H, Berk-Krauss J, Feng PW, et al. Comparison of dermatologist density between urban and rural counties in the United States. J*AMA Dermatol.* 2018;154:1265.
16. Mosnaim GS, Greenhawt M, Imas P, et al. Do regional geography and race influence the management of chronic spontaneous urticaria? *J Allergy Clin Immunol.* 2022;150:1260-1264.e7.
17. Giménez-Arnau AM, Alejo JV, Ramirez DM. Diagnostic and therapeutic management of chronic urticaria by dermatologists and the role of dermatology departments. *Actas Dermo-Sifiliográficas (Engl Ed).* 2015;106:528-532.
18. Ferrer M, Bartra J, Giménez-Arnau A, et al. Management of urticaria: not too complicated, not too simple. *Clin Exp Allergy.* 2015;45:731-743.
19. Melchers S, Nicolay JP. Chronic spontaneous urticaria—status quo and future. *Allergo J Int.* 2023;32:326-336.
20. Podder I, Dhabal A, Chakraborty SS. Efficacy and safety of up-dosed second-generation antihistamines in uncontrolled chronic spontaneous urticaria: a review. *J Clin Aesthet Dermatol.* 2023;16:44-50.
21. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on h1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol.* 2015;135:67-75.
22. Finlay AY, Kaplan AP, Beck LA, et al. Omalizumab substantially improves dermatology-related quality of life in patients with chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol.* 2017;31:1715-1721.

23. Omalizumab [package insert]. South San Francisco, CA: Genentech, Inc; 2024.
24. Kocaturk E, Saini SS, Rubiez CJ, Bernstein JA. Existing and investigational medications for refractory chronic spontaneous urticaria: safety, adverse effects, and monitoring. *J Allergy Clin Immunol Pract*. 2022;10:3099-3116.
25. Cyclosporine [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2023.
26. Soong W, Patil D, Pivneva I, et al. Disease burden and predictors associated with non-response to antihistamine-based therapy in chronic spontaneous urticaria. *World Allergy Organ J*. 2023;16:100843.
27. Yosipovitch G, Soares GB, Mahmoud O. Current and emerging therapies for chronic spontaneous urticaria: a narrative review. *Dermatol Ther (Heidelb)*. 2023;13:1647-1660.
28. Fok JS, Kolkhir P, Church MK, et al. Predictors of treatment response in chronic spontaneous urticaria. *Allergy*. 2021;76:2965-2981.
29. Sánchez-Borges M, Ansotegui IJ, Baiardini I, et al. The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations. *World Allergy Organ J*. 2021;14:100546.
30. Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): two randomized, double-blind, placebo-controlled, phase 3 trials. *J Allergy Clin Immunol*. Feb 29:S0091-6749(24)00196-9. doi: 10.1016/j.jaci.2024.01.028.
31. US Securities and Exchange Commission website. Regeneron press release. Available at:https://www.sec.gov/Archives/edgar/data/872589/000180422023000029/exhibit991q32023.htm. Accessed March 25, 2024.
32. Dupilumab [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2023.
33. ClinicalTrials.gov. Dupilumab for the treatment of spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are naïve to, intolerant of, or incomplete responders to omalizumab (LIBERTY-CSU CUPID). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04180488. Accessed April 9, 2024.
34. US Food & Drug Administration (FDA). Providing clinical evidence of effectiveness for human drug and biological products. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products. Accessed April 9, 2024.
35. Maurer M, Metz M, Anderson J, et al. Safety and clinical activity of multiple doses of barzolvolimab, an anti-KIT antibody, in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2023;151: AB133.
36. ClinicalTrials.gov. A phase 2 study of CDX-0159 in patients with chronic spontaneous urticaria. Available at: https://clinicaltrials.gov/study/NCT05368285. Accessed March 25, 2024.
37. Maurer M, Kobielusz-Gembala I, Mitha E, et al. Barzolvolimab significantly decreases chronic spontaneous urticaria disease activity and is well tolerated: top line results from a phase 2 trial. *J Allergy Clin Immunol*. 2024;153:AB366.
38. Maurer M, Berger W, Gimenez-Arnau A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria [published correction appears in *J Allergy Clin Immunol*. 2023;151:579]. *J Allergy Clin Immunol*. 2022;150:1498-1506.e2.
39. Maurer M, Gimenez-Arnau A, Jain V, et al. Remibrutinib treatment improves quality of life in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2022;149:AB179.
40. Maurer M, Gimenez-Arnau A, Ferrucci S, et al. Efficacy and safety of rilzabrutinib in patients with chronic spontaneous urticaria: 12-week results from the RILECSU phase 2 dose-ranging study. *J Allergy Clin Immunol*. 2024;153:AB373.
41. Maurer M, McLaren J, Chon Y, et al. Sustained improvement in UAS7 after 16-week treatment with tezepelumab in biologic-naïve adults with CSU: results of the phase 2b INCEPTION study. *J Allergy Clin Immunol*. 2024:153:AB373.
42. Altrichter S, Staubach P, Pasha M, et al. An open-label, proof-of-concept study of lirentelimab for antihistamine-resistant chronic spontaneous and inducible urticaria [published correction appears in *J Allergy Clin Immunol*. 2022;150:736-737]. *J Allergy Clin Immunol*. 2022;149:1683-1690.28.
43. ClinicalTrials.gov. A study to assess subcutaneous lirentelimab (AK002) in chronic spontaneous urticaria (MAVERICK). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05528861. Accessed March 25, 2024.
44. ClinicalTrials Arena. Allakos cuts employee count by half after two phase II failures. Available at: https://www.clinicaltrialsarena.com/news/allakos-cuts-employee-count-by-half-after-two-phase-ii-failures/. Accessed March 25, 2024.
45. Maurer M, Ensina LF, Gimenez-Arnau AM, et al. Efficacy and safety of ligelizumab in adults and adolescents with chronic spontaneous urticaria: results of two phase 3 randomised controlled trials. *Lancet*. 2024;403:147-159.
46. ClinicalTrials.gov. Study of efficacy and safety of ligelizumab in chronic spontaneous urticaria patients who completed a previous study with ligelizumab. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04210843. Accessed March 25, 2024.
47. Metz M, Kolkhir P, Alrtrichter S, et al. Mast cell silencing: A novel therapeutic approach for urticaria and other mast cell-mediated diseases. *Allergy*. 2024;79:37-51.
48. ClinicalTrials.gov. Study to assess the safety, tolerability, pharmacokinetics and immunogenicity of AK006 in healthy subjects and subjects with chronic spontaneous urticaria. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT06072157. Accessed March 25, 2024.
49. Chang C, Sharma A, Wells A, et al. Briquilimab, an anti-CD117 antibody, prevents passive systemic anaphylaxis in mice expressing chimeric human and mouse CD117 through mast cell depletion. *J Allergy Clin Immunol*. 2024;153:AB9.
50. Grassian A, Haidle A, AuDuong S, et al. BLU-808, a potent and selective small molecule inhibitor of wild-type c-KIT for mast cell disorders. *J Allergy Clin Immunol*. 2024;153:AB62.
51. ClinicalTrials.gov. Study evaluating the efficacy and safety of povorcitinib in adults with chronic spontaneous urticaria. Available: https://clinicaltrials.gov/study/NCT05936567. Accessed March 25, 2024.
52. Vitiligo society. Povorcitinib – what you need to know about this potential new treatment. Available at: https://vitiligosociety.org/vitlife/povorcitinib-what-you-need-to-know-about-this-potential-new-treatment/. Accessed March 25, 2024.
53. Maurer M, Abuzakouk M, Bérard F, et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. *Allergy*. 2017;72:2005-2016.
54. Yang CC, Chien WC, Chung CH, et al. The usage of histamine type 1 receptor antagonist and risk of dementia in the elderly: a nationwide cohort study. *Front Aging Neurosci*. 2022;14:811494.
55. Simon FER, Simons KJ. H1 Antihistamines: current status and future directions. *World Allergy Organ J*. 2008;1:145-155.
56. Guillén-Aguinaga S, Presa IJ, Aguinaga-Ontoso E, et al. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Brit J Dermatol*. 2016;175:1153-1165.
57. Sotés PI, Armisén M, Usero-Bárcena T, et al. Efficacy and safety of up-dosing antihistamines in chronic spontaneous urticaria: a systematic review of the literature. *J Investig Allergol Clin Immunol*. 2021;31:282-291.
58. Metz M, Vadasz Z, Kocatürk E, et al. Omalizumab updosing in chronic spontaneous urticaria: an overview of real-world evidence. *Clin Rev Allerg Immunol*. 2020;59:38-45.

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