Narrative Review Article

Therapeutic Approaches for Chronic Spontaneous Urticaria: Current and Emerging Options

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a recurrent, mast cell-mediated skin condition characterized by wheals, angioedema, or both lasting over six weeks without a known cause. Its underlying mechanisms are still being researched but involve some immune dysregulation, including Immunoglobulin E (IgE)-mediated mast cell activation and autoimmune signaling. This leads to unpredictable flare-ups that significantly affect a patient's quality of life. Current treatment guidelines recommend a stepwise approach. Second-generation H1-antihistamines are the first-line therapy, though many patients experience incomplete relief even after increasing the dosage. Omalizumab, an anti-IgE monoclonal antibody, is the standard second-line treatment and has transformed management for patients who do not respond to antihistamines by providing significant symptom control and improving quality of life. Dupilumab, which targets the Interleukin-4 (IL-4) and Interleukin-13 (IL-13) pathways, and Tezepelumab, which blocks thymic stromal lymphopoietin (TSLP), have shown substantial efficacy in recent trials, expanding biologics available for more severe cases of CSU. Emerging therapies continue to advance the field by targeting different points in mast cell activation. Remibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, and Barzolvolimab, an anti-KIT proto-oncogene, receptor tyrosine kinase (KIT) monoclonal antibody, has demonstrated promising results in reducing symptoms and improving disease control. Together, these treatments mark a shift towards precision medicine in CSU, focusing on targeted, mechanism-based therapies that not only improve symptom relief but also aim for long-term remission and reduced disease burden. This review focuses on approved and emerging biologic therapies for CSU from the past to present, with significant developments from 2014 to 2025.

Keywords: Chronic Spontaneous Urticaria; antihistamines; monoclonal antibodies; prescription treatments; mast cell activation; biologic therapy

INTRODUCTION

Chronic Spontaneous Urticaria (CSU) is a chronic inflammatory disease characterized by recurring wheals (also known as hives) and/or angioedema, which involves swelling of the lips, tongue, eyelids, or throat for more than 6 weeks (1, 2). Approximately 40% of CSU patients have accompanying episodes of angioedema. In contrast, 10% have symptoms of angioedema alone (3, 4). Clinically, CSU is scored along a 0-42 point scale, which measures the Urticaria Activity Score (UAS) over 7 days, called the UAS7 scale (5). It is calculated by summing the patient's UAS scores over a week, which are assigned a 0-3 score for the number

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of hives and a 0-3 score for itch severity each day (5). A higher UAS7 score typically indicates greater disease activity (5). CSU significantly affects a patient's quality of life and can be emotionally burdening. A recent meta-analysis showed that CSU patients are six times more likely to struggle with depression and anxiety than healthy people (6). It is also physically painful, which can impair performance at school or work. In a study involving 673 adult patients with CSU, more than 20% reported missing more than an hour of work per week, and 27% reported productivity impairment (7). Moreover, it is financially expensive. A study analyzing the healthcare costs of 6,350 urticaria patients reported that the mean annual healthcare cost was over $ 9,000 post-insurance (8). CSU is estimated to affect up to 1% of the world's population and is most common among women between 20 and 40 years old (9, 10).

CSU is generally caused by mast cell activation in specific signaling pathways. Mast cells are part of the immune system, and their primary role is to detect harmful invaders, such as pathogens (11, 12). Mast cells are produced in the bone marrow and travel through the blood to tissues (11, 12). When mast cells detect a potential hazard, they signal to recruit other immune cells by releasing chemical mediators, such as cytokines and histamine (13). When mast cells are activated unnecessarily, they trigger allergic reactions, such as CSU, through several mechanisms (13) (Figure 1). The exact triggers for CSU are unknown, hence the name "spontaneous" (14). Its counterpart, Chronic Inducible Urticaria, does have identifiable triggers, such as pressure and extreme temperatures, therefore making it distinct from CSU (15).

Two interconnected mechanisms are proposed to trigger mast cell activation: Type I autoimmunity, also known as autoallergy, and Type IIb autoimmunity (13). In healthy individuals, IgE antibodies, which are primarily associated with allergic reactions and parasite defense, bind to FcεRI receptors on mast cells and recognize foreign substances, called antigens (16). In CSU patients with Type I autoimmunity, these receptor-bound IgE antibodies begin to recognize self-antigens, molecules naturally present in the body that are not perceived as foreign under normal conditions (17, 18, 19). Once IgE antibodies bind to self-antigens, they trigger cross-linking of FcεRI, which brings two or more FcεRI receptors together, ultimately sending a strong activation signal to the mast cell and releasing inflammatory chemical mediators (16). The release of these mediators is what causes the symptoms associated with CSU. In Type IIb autoimmunity, IgG autoantibodies perform similarly to IgE autoantibodies, except they can bind to IgE antibodies themselves or FcεRI receptors to initiate cross-linking and the downstream signaling pathways (16). In addition, B-cell receptor signaling has been proposed to play a key role in CSU by promoting the generation of autoreactive B cells, those that recognize self-antigens and autoantibodies (13). B cells are white

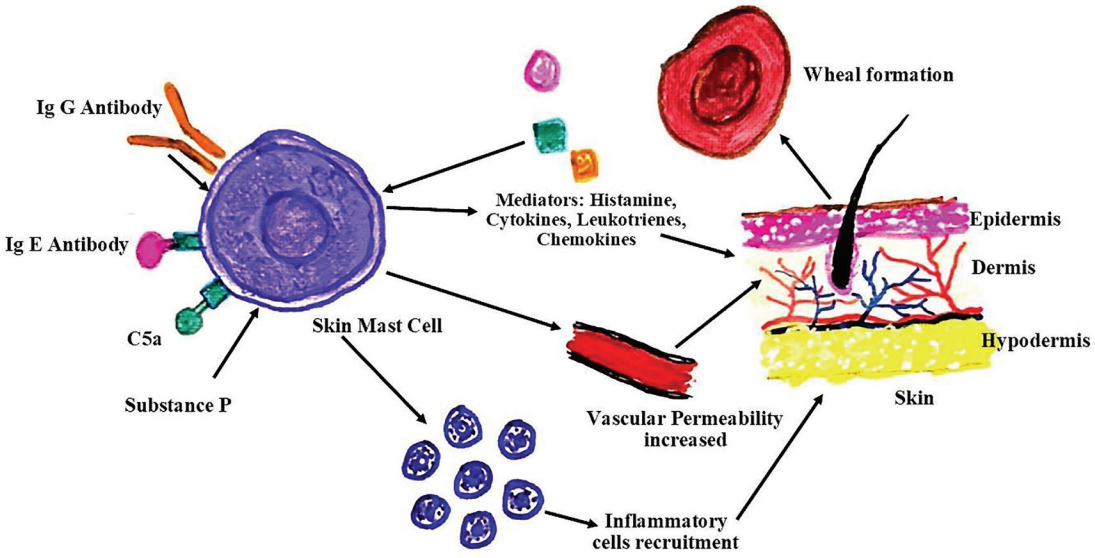

Figure 1. Mechanism and Pathophysiology of Chronic Spontaneous Urticaria. Painting Credit: Lakshmi N Kurnutala, MD, M.Sc. Professor of Anesthesiology, UMMC, Jackson, MS.

blood cells in the immune system that produce antibodies that bind to viruses and bacteria, preventing them from infecting healthy cells and effectively neutralizing them (20). Bruton tyrosine kinase (BTK), an intracellular protein that relays signals from cell surface receptors into the cell, plays a crucial role in FcεRI and B-cell receptor signaling; therefore, BTK inhibition is a potential target for CSU drugs (13). Few approved treatments are effective in treating CSU, but new ones targeting various pathways are emerging. In this paper, we will review approved and emerging treatments for CSU and analyze the strengths and weaknesses of current medications, highlighting significant developments in CSU treatment from 2014 to 2025 (Table 1).

Table 1. Management of Chronic Spontaneous Urticaria - Type of medication, mechanism, efficacy, FDA approval status, route of administration, cost for each dose, and side effect profile

Therapy	Mechanism	Efficacy	FDA-approval year	Route of administration	Cost per dose	Adverse effects
Second-generation H1-antihistamines (Cetirizine, Fexofenadine, Levocetirizine, Loratadine)	Block release of histamine on mast cells by blocking peripheral receptors	16% reached complete disease control in 2022 analysis of 582 patients	Before 2014	Oral	<1$	Drowsiness, fatigue, dry mouth, impaired driving at higher doses
Omalizumab (Xolair®)	Monoclonal antibody that binds to free IgE at the FcεRI binding site, blocking the free IgE from binding to FcεRI on mast cells and preventing signaling cascade	70% reached complete disease control after week 24 in 2011 double-blind, placebo-controlled trial	2014	Subcutaneous injection, typically every 4 weeks (150-300 mg)	$1420-$2800	Injection site reactions (pain, redness, or swelling), headache, risk of anaphylaxis (low), increased risk of viral infections
Dupilumab (Dupixent®)	Monoclonal antibody inhibiting IL-4/ IL-13 signalling by binding to IL-4 receptor alpha subunit, a shared receptor by IL-4 and IL-13 signaling pathways, preventing the cytokines from signaling through their receptor	Dupilumab treatment improved UAS7 over 12 and 24 weeks in 2 randomized, double-blind, phase 3 trials	2025	Subcutaneous injection, typically every 2 weeks (200-300 mg)	$2000	Injection site reactions, conjunctivitis, and possible increased risk of infections
Tezepelumab (Tezspire®)	Monoclonal antibody that binds to thymic stromal lymphopoietin (TSLP) cytokine, preventing it from binding to its receptor	Over a 16-32 week trial period, the medication improves itch and hive severity post-treatment in 2025 study	Off-label use for CSU	Subcutaneous injection, typically every 2 weeks (210-420 mg)	$4000-$8000	Rash, hives, sore throat, joint pain, back pain, injection site reactions, anaphylaxis

Continued Table 1. Management of Chronic Spontaneous Urticaria - Type of medication, mechanism, efficacy, FDA approval status, route of administration, cost for each dose, and side effect profile

Therapy	Mechanism	Efficacy	FDA-approval year	Route of administration	Cost per dose	Adverse effects
Remibrutinib (Rhapsido®)	Oral medication that inhibits Bruton's tyrosine kinase (BTK) enzymes, blocking release of histamine and other inflammatory mediators by mast cells	41.9% of patients achieved complete symptom reduction (UAS7 = 0) in 2022 randomized, double-blind trial. Well-controlled disease (UAS7 ≤ 6) was achieved in up to 55.8%	2025	Oral	Not yet available; cost unknown	Nasopharyngitis (cold-like symptoms), bleeding, headache, nausea, abdominal pain
Barzolvolimab	Monoclonal antibody that binds to the KIT proto-oncogene, receptor tyrosine kinase (KIT), inhibiting KIT activity in mast cells (which are KIT-positive in CSU patients)	71% of patients achieved a well-controlled response in 2021 phase 1b study, and 57% achieved complete symptom reduction (UAS7 = 0)	Not yet approved	Intravenous/ subcutaneous (depending on final formulation)	Not yet available; cost unknown	Hair color change, neutropenia, skin hypopigmentation (skin lightening), hives, nasopharyngitis (common cold)

APPROVED TREATMENTS FOR CHRONIC SPONTANEOUS URTICARIA

ANTIHISTAMINES

The first-line therapy for CSU is second-generation H1-antihistamines, such as Cetirizine (Zyrtec®), Loratadine (Claritin®), Fexofenadine (Allegra®), and Levocetirizine (Xyzal®) (21). These drugs work by inhibiting histamine release by selectively blocking peripheral receptors in the peripheral nervous system, thereby reducing adverse events (21). However, antihistamines may not provide enough relief for many CSU patients. A 2022 analysis assessing 582 CSU patients reported that only 16% reached complete-disease control (22). In addition, 37% of patients reported experiencing stress due to the unpredictable nature of the disease (22). Overall, 33% of patients transitioned to biologic therapy, with 26% of those patients switching to Omalizumab (Xolair®) (22).

OMALIZUMAB

For patients with more severe CSU, Omalizumab therapy is generally the next step. Omalizumab is the most established and widely used injectable biologic for CSU (23). It is a humanized, monoclonal anti-IgE antibody that binds to free IgE at the FcεRI binding site, thereby blocking free IgE from binding to FcεRI on mast cells and preventing the signaling cascade from occurring (23). Omalizumab's effectiveness was confirmed in many clinical trials, including a 2011 randomized, double-blind, placebo-controlled trial in which over 70% of participants with CSU experienced complete protection from wheals and a mean reduction in CSU symptoms by week 24, with adverse effects similar to those of the placebo group (24). It was approved by the FDA in 2014 for the treatment of CSU and costs $5,000 a month for commercially uninsured adults and $3,000 for commercially uninsured children. Despite Omalizumab's efficacy and FDA approval, a

subset of patients does not respond to it, underscoring the need for additional treatment options.

DUPILUMAB

Dupilumab (Dupixent®) is an additional treatment initially approved for moderate-to-severe eczema in 2017 (25). It was used off-label to treat CSU in patients nonresponsive to other medications until 2025, when it was FDA-approved in April 2025 specifically for CSU treatment. Dupilumab is an injectable monoclonal antibody that blocks the effects of interleukin-4 (IL-4) and interleukin-13 (IL-13), cytokines released by mast cells (26). The medication binds to the IL-4 receptor alpha subunit (IL-4Rα), the receptor shared by the IL-4 and IL-13 signaling pathways, thereby preventing cytokine signaling through their receptors and reducing inflammation and CSU symptoms (26). A study comprising two phase 3, randomized, placebo-controlled, double-blind trials comparing Dupilumab with placebo in CSU patients found that Dupilumab significantly reduced itch and hive severity in patients who did not respond to antihistamines but were Omalizumab-naive. Those who had previously been introduced to both treatments showed minimal improvement with Dupilumab (27). In another study, however, testing the long-term effects of Dupilumab, six patients who failed to respond to Omalizumab at high doses for prolonged periods were selected. After receiving Dupilumab and then discontinuing it for 22 months, 4 of the 6 patients achieved CSU remission, suggesting it is a promising long-term treatment. Still, more studies are needed to confirm its efficacy (26). The cost of dupilumab ranges from $3,800 to $4,000 per carton for commercially uninsured patients (28).

TEZEPELUMAB

Tezepelumab (Tezspire®) was approved by the FDA in 2021 to treat severe asthma, and currently it is used to treat CSU as an off-label medication by physicians. It is an injectable monoclonal antibody that targets thymic stromal lymphopoietin (TSLP), a cytokine released by mast cells (29). Tezepelumab directly binds TSLP, preventing it from binding its receptor and thereby inhibiting an inflammatory response (29). A 2025 phase 2b study with 183 patients investigated the impact of Tezepelumab on CSU patient symptoms (30). Of the 183 patients, 125 had not received Omalizumab treatment previously, while 58 had (30). Over the 16-week trial period, Tezepelumab did not significantly improve itch and hive severity compared to placebo in patients, but did improve itch and hive severity post-treatment through week 32, suggesting a delayed and sustained treatment effect (30). Its listed price is over $4,300 per dose for commercially-uninsured patients (31). Although currently approved therapies, including omalizumab and dupilumab, have significantly improved CSU management, incomplete responses and relapse in a subset highlight the need for additional approaches. There are few emerging therapies now under investigation aiming to address these gaps by modulating alternative immune pathways, offering promise for more comprehensive disease control.

EMERGING TREATMENTS FOR CHRONIC SPONTANEOUS URTICARIA

REMIBRUTINIB

One of the emerging treatments is an oral drug called Remibrutinib (Rhapsido®), a small-molecule inhibitor of BTK approved by the FDA in September 2025 for CSU (32, 33). BTK enzymes trigger mast cells to release histamine and other inflammatory mediators, leading to the symptoms of CSU (32, 33). Thus, inhibiting these BTK enzymes could reduce such symptoms (32, 33). A 2022 randomized, double-blind, placebo-controlled trial testing the efficacy of Remibrutinib showed that fewer symptoms were observed in the 281 patients who completed the trial from week 1 through week 12, the entire period during which the drug was administered (32). By week 12, up to 41.9% of patients receiving Remibrutinib achieved complete symptom reduction (UAS7 = 0), compared to 14.3% in the placebo group (32). Additionally, well-controlled disease (UAS7 ≤ 6) was achieved in up to 55.8% of remibrutinib-treated patients versus 28.6% in the placebo group (32). To test Remibrutinib's long-term safety in CSU, 230 patients who previously participated in the 2022 trial (32) were enrolled in a follow-up phase 2b extension study (33). Patients with a UAS7 score ≥16 entered the treatment period and received Remibrutinib 100 mg twice daily for 52 weeks (33). Those with a UAS7 ≤6 were monitored without treatment during an observational period (33). Thirty-four of these patients experienced a relapse and transitioned into the treatment period (33). At baseline, the mean UAS7 was 27.9, indicating moderate to severe Urticaria activity (33). By Week 4, 52.7% of patients achieved a UAS7 score of ≤6, and 28.2% achieved a UAS7 score of 0 (33). By Week 52, these numbers improved to 68.0% and 55.8%, respectively (33). The most common adverse effects included infections, skin

and subcutaneous tissue disorders, and gastrointestinal disorders at prevalence rates of 30.9%, 26.8%, and 16.5%, respectively (33). Most adverse events were mild or moderate (33).

BARZOLVOLIMAB

Another developing treatment is Barzolvolimab, an injectable monoclonal antibody that targets mast cells expressing the KIT proto-oncogene, receptor tyrosine kinase (KIT) (34, 35). The mast cells that cause CSU are KIT-positive (35). By binding to KIT receptors, Barzolvolimab inhibits their activity, leading to mast cell depletion and reduced mediator production (35). In a 2025 phase 1b, double-blind, placebo-controlled trial, 42 patients with a high mean baseline of CSU activity showed rapid symptom reduction in 1 week and sustained reduction by 12 weeks (34). Additionally, 71% of these patients achieved well-controlled Urticaria, with symptoms decreasing significantly, and 57% achieved a complete response with total symptom reduction (34). Multiple doses of Barzolvolimab were well tolerated, and patients responded similarly with or without prior Omalizumab exposure (34). The most common adverse event was hair color change, with 26% of patients experiencing changes on the scalp, beard, and/or body (34). These results showed that Barzolvolimab could be a promising treatment for CSU patients who did not respond desirably to Omalizumab (34).

CONCLUSION

CSU is a debilitating condition that profoundly affects patients' quality of life. Although multiple therapeutic options are available, treatment responses vary considerably, underscoring the importance of individualized management strategies. This review examines current and emerging treatments for CSU and assesses their efficacy, advantages, and shortcomings in comparison to one another.

One significant advantage of approved treatments such as Omalizumab, Dupilumab, and Tezepelumab is their proven reliability. Since these treatments have received FDA approval, they have been rigorously tested and have demonstrated success in many patients, indicating their safety and a low risk of complications. Omalizumab, in particular, is regarded as one of the most reliable biologics. A 2011 study showed that the adverse effects of Omalizumab did not differ significantly from those in the placebo group. Given that emerging treatments like Remibrutinib and Barzolvolimab are still undergoing clinical testing for efficacy, approved biologics may be a more viable option for some patients.

However, the high costs of approved treatments, which can reach thousands of dollars, often pose a barrier for many Americans who are commercially uninsured. In contrast, clinical trials for emerging drugs frequently provide treatment at no cost to participating patients. Nevertheless, these trials often have strict eligibility criteria, such as excluding patients who have previously received Omalizumab. Additionally, expenses not directly related to the trials, like transportation and lodging, are typically not covered, which can be a drawback for patients considering emerging therapies.

Despite these challenges, emerging drugs show great promise. For example, a 2022 randomized trial and a 2019-2022 extension study demonstrated that Remibrutinib was highly effective in reducing CSU symptoms with very mild side effects. The extension study further confirmed that Remibrutinib maintained a favorable safety profile with sustained efficacy. Barzolvolimab also showed promise, as seen in the 2025 phase 1b study. However, this study found that hair color changes were the most common side effect reported by patients, which is worth considering.

Another vital distinction between treatments is the method of administration. Unlike most injectable drugs, Remibrutinib is taken orally, which may improve ease of use for specific patients and could be appealing for those seeking non-injectable alternatives.

Returning to approved therapies, one limitation of Dupilumab is that some patients may not respond significantly if they have previously been treated with Omalizumab, as indicated in a 2024 study combining two Phase 3 trials. Another limitation is that Tezepelumab is not yet FDA-approved for the direct treatment of CSU. Therefore, it is often prescribed off-label and is typically not covered by insurance. While manufacturer assistance programs exist for Tezepelumab and other approved drugs that provide medications at no cost or at reduced cost to uninsured or underinsured patients, the eligibility criteria must be met. These requirements usually include proof of permanent U.S. residency, insurance status, and a demonstrated need for financial assistance. Such criteria can drastically reduce the eligible patient pool, as many Americans may not qualify. Insurance can cover on-label CSU treatments, but patients must meet specific requirements outlined in their insurance plan's medical

policy. Additionally, coverage often escalates based on the patient's response to the treatment, with initial coverage determined by official diagnostic guidelines for CSU. These guidelines define the necessary evidence or test results required for coverage eligibility.

In conclusion, both approved and emerging treatments for CSU hold promise, but each has significant side effects that patients must consider. Chronic spontaneous urticaria significantly impacts patients' quality of life and remains an area of active research. The ongoing development of more effective, accessible, and personalized treatments is essential to ensure that all patients can achieve sustained relief.

CONFLICT OF INTERESTS

The author declares no conflicts of interest related to this work.

ABBREVIATIONS

CSU	Chronic Spontaneous Urticaria
UAS	Urticaria Activity Score
IgE	Immunoglobulin E
IgG	Immunoglobulin G
BTK	Bruton tyrosine kinase
FDA	Food and Drug Administration
TSLP	Thymic stromal lymphopoietin
KIT Receptor	Receptor Tyrosine Kinases

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