Journal of Inflammation Research

Dovepress
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REVIEW

Treatment Approaches for Omalizumab-Refractory Chronic Spontaneous Urticaria

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Abstract: Chronic spontaneous urticaria (CSU) is a mast cell–driven disease that impairs health-related quality of life. Although omalizumab is a cornerstone treatment for patients uncontrolled with up-dosed second-generation H1-antihistamines, some patients remain partially responsive or refractory. This narrative review summarizes current concepts in defining, predicting, and managing omalizumab-refractory CSU. Response assessment should rely on validated patient-reported outcome measures, particularly the 7-day Urticaria Activity Score (UAS7) and Urticaria Control Test (UCT), to distinguish complete response, partial response, and true non-response, while also helping to identify pseudo-resistance related to poor adherence or misdiagnosis. Emerging biomarker data support an endotype-driven approach: higher total immunoglobulin E (IgE) is generally associated with type I autoallergic CSU and a better response to omalizumab, whereas low total IgE, basopenia, positive basophil histamine release assay (BHRA) or basophil activation test (BAT) results, and other autoimmune markers suggest type IIb autoimmune CSU and a greater likelihood of inadequate anti-IgE response. For patients with persistent disease despite omalizumab, cyclosporine A remains an evidence-based option, while newer targeted therapies, including dupilumab, Bruton's tyrosine kinase inhibitors, and anti-KIT antibodies, are expanding the treatment landscape. Overall, management of omalizumab-refractory CSU is shifting toward precision medicine that integrates validated outcome measures, biomarker-informed endotyping, comorbidities, access, safety, and patient preferences. However, standardized switching algorithms, comparative effectiveness data, and validated predictive biomarkers are still needed to optimize individualized care.

Keywords: biomarkers, chronic urticaria, omalizumab, patient-reported outcome measures, therapeutics

Introduction

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous development of wheals, angioedema, or both for more than 6 weeks, without a definite eliciting factor.[1] The pathophysiology of CSU is multifactorial, involving complex interactions among autoimmune mechanisms, complement activation, coagulation pathways, and inflammatory pathways. Current evidence supports the presence of two principal CSU endotypes, both characterized by mast cell–activating autoantibodies: (1) type I or autoallergic, driven by immunoglobulin E (IgE) autoantibodies against self-antigens and (2) type IIb or autoimmune, mediated by immunoglobulin G (IgG) autoantibodies targeting the high-affinity IgE receptor (FcεRI) or IgE. These mechanisms converge on mast cell activation but differ in therapeutic responsiveness.[2] The global point prevalence of CSU is estimated at 0.7%.[3] CSU imposes a substantial burden through high treatment costs, healthcare resource use, productivity loss, and impaired health-related quality of life (HR-QoL), including effects on sleep, work, and social activities.[4]

https://doi.org/10.2147/JIR.S554124
Received: 11 March 2026
Accepted: 29 May 2026
Published: 19 June 2026

Omalizumab is a cornerstone treatment for CSU. It binds circulating IgE, reducing its levels and promoting down-regulation of FcεRI on mast cells and basophils, thereby increasing their activation threshold and limiting degranulation. This disrupts IgE-mediated mast cell activation and decreases the release of inflammatory mediators. Additionally, IgE–omalizumab complexes may sequester autoantigens and anti-IgE autoantibodies, while binding to membrane IgE on B cells may reduce ongoing IgE production, further attenuating activity along the IgE–FcεRI–mast cell pathway.[5] Because omalizumab targets the IgE–FcεRI axis, it is generally more effective in patients with the type I autoallergic endotype of CSU, in which IgE autoantibodies play a central pathogenic role. In contrast, patients with type IIb autoimmune CSU tend to exhibit a slower and often less robust response to anti-IgE therapy.[2]

Clinical trials demonstrated symptom reduction in 52–66% of patients, while real-world data indicate response rates up to 85%, with 68% achieving complete remission.[6,7] Consequently, omalizumab has been the therapy of choice for patients who remain refractory to high-dose second-generation H1-antihistamines (sgH1AH) since 2016.[1] However, for patients who do not respond to omalizumab, cyclosporine A (CsA) was, until recently, the only available option supported by sufficient clinical evidence of efficacy, albeit with the risk of significant adverse effects, particularly with long-term use.[8]

With improved understanding of CSU pathophysiology and the development of new targeted therapies, options for patients with inadequate response to omalizumab are expanding. However, post-omalizumab management remains challenging because definitions of inadequate response, predictive biomarkers, and switching algorithms are not yet standardized. Here, we summarize strategies for assessing omalizumab response and discuss current and emerging options for omalizumab-refractory CSU. The literature was identified through targeted searches of PubMed/MEDLINE and Google Scholar, supplemented by international guidelines, key clinical trials, systematic reviews, and relevant recent reviews. No formal risk-of-bias assessment or meta-analysis was performed.

Definition of Response to Omalizumab

CSU management has undergone a profound transformation, moving away from a reactive, symptom-based approach toward a proactive, goal-oriented strategy focused on complete disease control and normalization of HR-QoL.[8] Because CSU is unpredictable, with spontaneous remissions and recurrent lesions, defining response is challenging. Defining response, timing assessment, and distinguishing response speed and depth are essential for precision-based care.[9] Most response definitions are based on omalizumab,[10] sgH1AH,[11] or CsA[12] and may not fully apply to newer treatments. Defining response in CSU requires moving from subjective impressions to validated patient-reported outcome measures (PROMs) that capture disease activity, disease control, and HR-QoL impact.[13]

Time to Evaluate Response

Response assessment should reflect the expected onset of action of each therapy.[14] Standardized evaluation windows prevent premature switching. In the case of sgH1AH, the evaluation window for initial response evaluation is 2 to 4 weeks.[15,16] If the patient remains symptomatic after this period, the dose can be increased up to four-fold the standard licensed dose. A definitive evaluation of response to high-dose sgH1AH should again occur after 2 to 4 weeks of the up-dosed regimen. Patients who do not achieve a 7-day Urticaria Activity Score (UAS7) ≤6 or an Urticaria Control Test (UCT) score ≥12 after this duration are classified as sgH1AH-refractory and qualify for second-line therapy.[17]

In the case of omalizumab, a longer evaluative period is required due to its mechanism of action involving the sequestration of free IgE and the subsequent downregulation of FcεRI receptors on mast cells and basophils. Expert consensus suggests the following timeline for response assessment:

- Early assessment (4−6 weeks): This identifies fast responders who achieve early control.[17]
- Standard evaluation point (12 weeks): Physicians should determine if the patient has achieved a complete, partial, or non-response after the third injection. This is also an appropriate time point to consider a skin biopsy if diagnosis is questioned because of lack of response to omalizumab.[17,18]
- Extended trial period (24 weeks): For patients who show a partial or slowly improving response, the trial should be extended to at least six months before concluding that the drug is ineffective.[6]

Fast versus Slow Response

Fast responders constitute approximately 70% of patients responding to omalizumab. These patients improve within days to 1−4 weeks after the first injection.[17] Slow or late responders do not demonstrate significant improvement until 12−14 weeks. Although low IgE levels are associated with reduced response to omalizumab, a considerable proportion of patients with severe CSU and low IgE levels may still show a rapid response, indicating that IgE levels alone are not definitive predictors of treatment outcome.[19] Therefore, response speed alone should not be used to define a CSU phenotype. One possible explanation for the rapid response observed in some patients with type IIb CSU[20] is that omalizumab may detach IgE and inhibit downstream signaling pathways.

Non-Response versus Partial Response

Complete control of CSU is defined as the absence of signs and symptoms while the patient remains on treatment. Good control corresponds to low disease activity with minimal impairment in HR-QoL, whereas partial control reflects persistent active disease with a relevant impact on HR-QoL. Absence of control is assumed when criteria for complete, good, or partial control are not fulfilled, indicating the need for treatment adjustment. These response categories should be determined using validated PROMs.[14]

Patient-Reported Outcome Measures (PROMs)

Validated PROMs are increasingly emphasized because they provide standardized assessment in both clinical trials and routine practice.[1,21] Their use at each visit is recommended.[1,22] PROMs support timely treatment transitions, particularly for non-responders.

Disease Activity Instruments

The Urticaria Activity Score (UAS) is the gold standard for assessing daily disease activity and is recorded once daily. It captures the number of wheals and pruritus intensity, each scored from 0 to 3, resulting in a maximum daily score of 6. The UAS7 represents the sum of daily scores over 7 consecutive days, resulting in a total score of 0 to 42.[1,21,23] UAS7 values of ≤6 are generally considered to reflect minimal disease activity, whereas scores of ≥16 and ≥28 are indicative of moderate and severe disease activity, respectively.[24] The UAS requires a high level of patient compliance and does not capture angioedema. The Angioedema Activity Score (AAS) consists of five daily questions, each scored from 0 to 3, with a maximum daily score of 15 and a weekly maximum of 105. The AAS28, a 4-week cumulative score, is used to assess long-term angioedema activity.[1,25]

Disease Control Instruments

The UCT evaluates disease control in patients who develop wheals, with or without angioedema.[1] It is a 4-item retrospective questionnaire that evaluates symptom burden, HR-QoL impact, perceived treatment effectiveness and the patient's overall perception of disease control over the previous 4 weeks.[26] Each item is scored from 0 to 4, with a total score ranging from 0 to 16. A score ≥12 indicates well-controlled urticaria, while a score of 16 reflects complete control.[1,27] The UCT helps guide treatment escalation. The Angioedema Control Test (AECT) assesses disease control in patients who experience angioedema, with or without wheals. It is a retrospective questionnaire consisting of 4 questions. A score ≥10 indicates well-controlled angioedema. Two validated versions are available, with recall periods of 4 weeks and 3 months.[1,24,28]

Health-Related Quality of Life (HR-QoL) Instruments

CSU affects functional capacity (including sleep, work, and social activities) and patients' emotional and psychological well-being.[1,4,29] To assess HR-QoL impairment in CSU, the Chronic Urticaria Quality of Life (CU-Q2oL) and the Angioedema Quality of Life (AE-QoL) questionnaire can be used.[1]

Defining Omalizumab Non-Response Using PROMs

In clinical practice and trials, patients are generally considered treatment non-responders if they fail to achieve meaningful improvement in disease activity or control, reflected by persistent UAS7 ≥16 and/or UCT <12. Complete response is usually defined as UAS7 = 0 and UCT = 16.[21] In omalizumab-refractory patients, the integration of multiple PROMs is essential for distinguishing non-responders from partial responders. PROMs may also be useful in raising suspicion of pseudo-resistance, for example in cases of poor treatment adherence, misdiagnosis, or psychiatric comorbidities. We summarize criteria for treatment response in Table 1.

Biomarkers of Response to Omalizumab

In CSU, numerous biomarkers have been investigated to predict response to omalizumab. An ideal biomarker should demonstrate high sensitivity and specificity, reproducibility, feasibility for routine clinical use, and broad validity across patient populations.[30] Currently, accessible markers such as total IgE, blood basophil counts, D-dimer, and IgG anti-thyroid peroxidase (anti-TPO) antibodies may support clinical endotyping when interpreted alongside disease activity and comorbidities. Functional basophil assays, cytokine and complement markers, and detailed autoantibody profiling remain largely investigational or restricted to specialized centers. The following sections summarize the main biomarker groups proposed to predict omalizumab response and their clinical limitations.

Total IgE and IgE/FcεRI–Related Markers

Total IgE and FcεRI-related markers are central to CSU biomarker research and may inform endotyping and omalizumab response, although they are insufficient as standalone switching tools.[31] Approximately half of patients with CSU have elevated total IgE, but levels vary widely.[32] High baseline IgE typically identifies a type I autoallergic endotype characterized by rapid, optimal responses to omalizumab and a higher risk of relapse upon withdrawal, whereas low total IgE frequently signals a type IIb autoimmune profile associated with IgG/IgM autoantibodies, antinuclear antibodies (ANA) or IgG anti-TPO positivity, and significant resistance to both sgH1AH and omalizumab.[33] Although recent data suggest that higher IgE levels (often with a predictive cutoff around 60 IU/mL) correlate with better treatment outcomes, the reliability of these markers remains inconsistent across different populations.[9,34]

Basophil-Related Biomarkers

Basophil-related biomarkers provide mechanistic insights into CSU endotypes and treatment response.[32,35] Basophil counts in the blood typically show an inverse relationship with disease activity, as these cells are recruited from the circulation into active skin lesions during flares.[36] Consequently, basopenia is frequently observed in patients with high UAS7 scores and type IIb autoimmune features.[37] In clinical practice, low baseline basophil levels often signal a higher risk of sgH1AH resistance and a poor or delayed response to omalizumab, while the normalization of these counts serves as a dynamic indicator of successful symptom control.[38]

Table 1 Validated PROMs for Assessing Disease Activity, Control, and Impact in CSU

	Complete Response	Good Response	Partial Response	MCID
UAS7	0	1-6	>6	≥10
AAS28	N/A	N/A	N/A	8-10
UCT	16	≥12	<12	≥3
CU-Q2oL	N/A	N/A	N/A	≥10

Abbreviations: AAS28, 28-day Angioedema Activity Score; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life questionnaire; MCID, Minimal Clinically Important Difference; N/A, not applicable; PROMs, Patient-Reported Outcome Measures; UAS7, 7-day Urticaria Activity Score; UCT, Urticaria Control Test.

Functional assays such as the Basophil Histamine Release Assay (BHRA) provide insight into the underlying type IIb autoimmune drivers of the disease, with a positive BHRA supporting a type IIb autoimmune endotype.[39,40] Patients with this profile often experience more severe, treatment-refractory disease; they tend to respond slower to omalizumab but may show better efficacy with CsA.[39–41]

The Basophil Activation Test (BAT) further refines endotyping by using flow cytometry to measure the expression of activation markers like CD63 and CD203c.[42] Positive BAT results are highly associated with the autoimmune cluster of CSU that is characterized by low IgE, positive IgG anti-TPO, and basopenia, and correlate with a significantly higher risk of omalizumab failure.[43] Although tracking dynamic changes in BAT throughout therapy can help monitor treatment response, the need for fresh blood samples and the lack of global standardization currently limits its routine use as a standalone tool for managing refractory cases.[44]

Coagulation and Systemic Inflammation Markers

The activation of the extrinsic coagulation pathway is a hallmark of CSU pathobiology. Activated eosinophils and monocytes express tissue factor, which triggers thrombin generation; this thrombin then directly amplifies mast-cell degranulation and wheal formation.[45] D-dimer, a fibrin degradation product, serves as the primary marker for this process.[46] It correlates with UAS7 severity scores and acts as a dynamic indicator of disease activity, typically normalizing when a patient enters remission.[47] High baseline D-dimer levels often flag severe, refractory disease and may identify patients who require anticoagulation or alternative biologics due to incomplete omalizumab control.[48]

Inexpensive, blood-based composite indices capture the imbalance between innate and adaptive immunity during CSU flares. Markers such as the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and the Systemic Immune-Inflammation Index (SII) tend to rise with disease activity and normalize in omalizumab responders.[49,50] These indices, particularly a baseline NLR greater than 3, have shown a better ability to predict early treatment response than isolated C-reactive protein (CRP), though they still lack the specificity of more targeted markers like D-dimer in complex multivariate models.[50]

Complement–eosinophil crosstalk may also contribute.[45,51] C5a levels rise during active flares, promoting degranulation independently of the FcεRI receptor, which may explain why some patients do not respond to IgE-targeted therapies.[45] Similarly, eosinophil cationic protein (ECP) tracks with disease flares and links to coagulation activation in autoimmune endotypes. However, their clinical utility is limited by a lack of validated cut-offs.[51,52]

Emerging multi-omics approaches and composite ratios, such as D-dimer/albumin and fibrinogen/albumin ratio, may improve diagnostic accuracy beyond traditional markers in CSU.[53] Additionally, molecular signatures such as upregulated STAT3 expression are associated with low-IgE autoimmune profiles.[54] However, these promising biomarkers require prospective validation before informing treatment decisions in omalizumab-refractory patients.[52–54]

Other Autoimmune/Emerging Biomarkers

Additional autoimmune biomarkers may help define CSU endotypes, although they lack prospective validation as guides for switching therapy.[41,55] The presence of IgG anti-TPO and ANA serves as a primary indicator of autoimmune CSU.[56,57] Present in 15–30% of cases, these markers are typically associated with low total IgE, basopenia, and a diminished response to omalizumab.[56] Research suggests that the IgG anti-TPO/total IgE ratio is a particularly strong predictor; a ratio exceeding 0.4–0.6 significantly increases the odds of treatment non-response and post-treatment relapse.[57] Similarly, the Autologous Serum Skin Test (ASST) remains a valuable, if subjective, tool for confirming the presence of functional IgG autoantibodies that drive delayed treatment responses.[55,56]

In contrast, the identification of IgE autoantibodies against self-antigens, such as IL-24, characterizes the type I autoallergic endotype.[55] Anti-IL-24 IgE is nearly universal in CSU patients and correlates with disease severity, yet these patients often remain highly responsive to omalizumab.[58] Distinguishing between these IgE autoantibodies and IgG-driven autoimmunity is essential, as high IgE levels often predict the rapid, complete responders, while the absence of these markers combined with positive classical autoimmune signals points toward more refractory disease.[35,56]

Limitations of Current Evidence and Unmet Needs

Biomarker evidence in CSU remains limited by methodological and translational challenges. Most studies are small, retrospective, and single-center, with inconsistent definitions of treatment response, variable UAS7 thresholds, and different follow-up timepoints.[59] Additionally, heterogeneous omalizumab treatment regimens further complicate comparisons across studies and populations.

Technical barriers also hinder reproducibility. Assays for critical signals like D-dimer, BAT, and IgE are not standardized across laboratories, leading to inter-laboratory variability that can exceed 30%.[60] Functional tests, such as the BHRA or BAT, remain largely confined to specialized research centers because they require fresh blood and high-level operator expertise.[61] Furthermore, while dynamic markers such as the decline of D-dimer or the normalization of basophil counts during treatment show stronger predictive signals than baseline snapshots,[48,62] they require longitudinal sampling that is rarely performed in standard real-world care.

CSU heterogeneity limits predictive performance. While markers can partially distinguish between the type I autoallergic and type IIb autoimmune CSU, over 40% of patients exhibit mixed features.[63,64] This overlap results in area under the curve (AUC) values of 0.65–0.75, which are insufficient for a clinician to rely on as a sole decision-making tool.[65] Even composite indices (combining markers like the IgG anti-TPO/IgE ratio with basophil counts) modestly improve accuracy but fail to reliably predict a patient's specific need for dose escalation or their likelihood of responding to alternative treatments.[9,40] Validated algorithms and feasible biomarker panels are needed. The future of CSU management lies in prospective randomized controlled trials that stratify refractory patients by their biomarker profiles. Table 2 summarizes key biomarker profiles associated with distinct CSU endotypes and outlines potential therapeutic considerations.

Management of Omalizumab-Refractory CSU: Current and Emerging Therapies

Although omalizumab is effective for many patients with CSU, a significant subset remains partially responsive or refractory, as defined by persistent activity on validated PROMs. The integration of tools such as UAS7, UCT, and emerging biomarkers has improved identification of true non-responders and highlighted disease heterogeneity beyond the IgE–FcεRI axis. This has driven interest in therapies targeting alternative pathogenic pathways, including type 2–mediated inflammation, autoantibody-driven mechanisms, and intracellular signaling cascades. These agents may provide more personalized options after omalizumab failure. Figure 1 summarizes a practical treatment algorithm for patients with CSU uncontrolled despite up-dosed sgH1AH. Post-omalizumab treatment selection should consider clinical profile,

Table 2 Biomarker-Guided Endotyping and Therapeutic Selection in Omalizumab-Refractory CSU

Biomarker Profile	Likely Endotype	Therapeutic Considerations	Explanation
High total IgE (>100 IU/mL)	Type I autoallergic	Omalizumab (standard or high dose)	Rapidly neutralizes free IgE and prevents auto-allergen cross-linking
Low total IgE (<40 IU/mL) + positive IgG anti-TPO/ANA	Type IIb autoimmune	BTK Inhibitors (e.g, remibrutinib) or CsA	Bypasses the IgE-neutralization step to block downstream IgG-mediated signaling
Basopenia + positive BAT/BHRA	Type IIb autoimmune	CsA	Addresses the systemic recruitment and hyper-responsiveness of cells in autoimmune profiles
High D-dimer/high CRP	Systemic/coagulation axis	Omalizumab (high dose) or dupilumab	High inflammation often requires higher doses; dupilumab targets the Th2 cytokine milieu (IL-4/IL-13)
High C5a/positive ASST	Complement-driven	CsA or C5a blockers (investigational)	Addresses IgE-independent mast cell degranulation pathways

Abbreviations: ANA, antinuclear antibodies; ASST, Autologous Serum Skin Test; BAT, Basophil Activation Test; BHRA, Basophil Histamine Release Assay; BTK, Bruton's tyrosine kinase; CRP, C-reactive protein; CsA, cyclosporine A; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G; IL-4, interleukin-4; IL-13, interleukin-13; TPO, thyroid peroxidase.

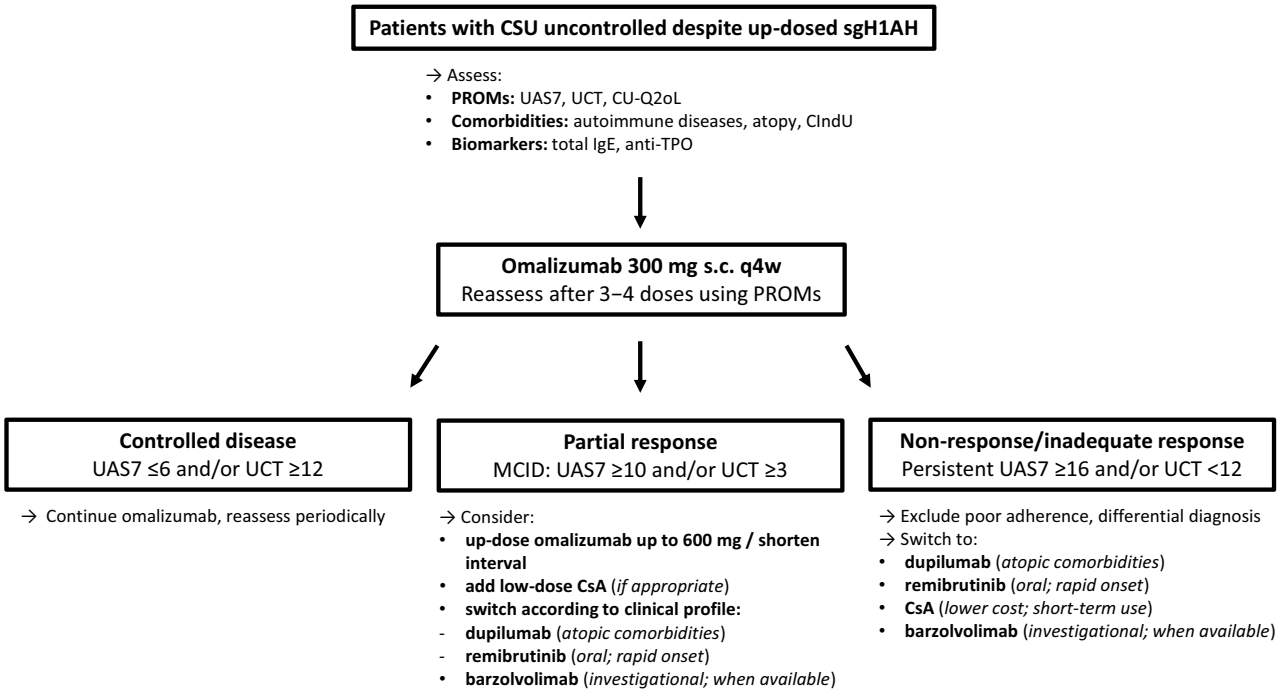

Figure 1 Proposed practical treatment algorithm for patients with CSU uncontrolled despite up-dosed sgH1AH. Baseline assessment includes PROMs, comorbidities, and selected biomarkers. After omalizumab 300 mg s.c. q4w, response is reassessed after 3–4 doses using PROMs to guide continuation, optimization, or switching of therapy. **Abbreviations**: CsA, cyclosporine A; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; CIndU, chronic inducible urticaria; MCID, Minimal Clinically Important Difference; PROMs, Patient-Reported Outcome Measures; q4w, every 4 weeks; s.c., subcutaneous; sgH1AH, second-generation H1-antihistamines; anti-TPO, IgG anti-thyroid peroxidase; UAS7, 7-day Urticaria Activity Score; UCT, Urticaria Control Test.

comorbidities, safety, access, and patient preferences. CsA remains an established option but requires monitoring. Dupilumab may be favored in patients with type 2 comorbidities, whereas remibrutinib offers a rapid oral option, and anti-KIT therapy, particularly barzolvolimab, remains investigational.

Dupilumab: Targeting Type 2 Inflammation in CSU

CSU exhibits a type 2 helper T-cell (Th2)-skewed immune profile within its perivascular dermal infiltrate, characterized by increased expression of cytokines such as interleukin (IL)-4, IL-5, IL-13, IL-31, and IL-33. These mediators promote IgE class switching, upregulate FcεRI expression on mast cells and basophils, enhance eosinophil recruitment and survival, and contribute to pruritus and vascular inflammation. Their increased expression in lesional skin supports a localized type 2 milieu that may amplify wheal formation.[66]

Dupilumab is a fully human IgG4 monoclonal antibody that binds to the interleukin-4 receptor alpha (IL-4Rα) subunit, a shared component of the IL-4 and IL-13 receptor complexes expressed on multiple immune cells, including T and B lymphocytes. By blocking IL-4Rα–mediated signaling, dupilumab inhibits the biological activity of both IL-4 and IL-13, two key cytokines driving the Th2 inflammatory response.[2]

In the Phase 3 LIBERTY-CSU CUPID A and C studies, dupilumab significantly improved disease control in omalizumab-naïve patients with CSU uncontrolled by sgH1AH. At week 24 in the pooled population, well-controlled CSU (UAS7 ≤6) was achieved by 43.1% of patients treated with dupilumab compared with 23.4% in the placebo group, and complete control occurred in 30.6% versus 15.9%, respectively; additionally, UCT scores increased significantly, supporting improved overall disease control. In Study A, the sustained efficacy of dupilumab was maintained throughout the off-treatment follow-up period to week 36, indicating persistence of clinical benefit beyond the 24-week treatment phase.[67,68]

Dupilumab responses were observed regardless of baseline total IgE levels, with consistent improvements in urticaria activity in patients with IgE concentrations both below and above predefined cutoffs (eg, 40 IU/mL and 60 IU/mL). Additionally, treatment efficacy was comparable irrespective of the presence of common atopic comorbidities, indicating

that dupilumab's therapeutic benefit in CSU is not restricted to patients with elevated IgE or an atopic background.[69] Improvement in HR-QoL was also demonstrated, with reductions versus placebo in CU-Q2oL (−8.6) scores by week 24. More dupilumab-treated patients reported "no or little" impact of CSU on daily activities.[67]

Across CUPID studies, the safety findings aligned with the established dupilumab safety profile, with treatment-emergent adverse events occurring at comparable rates between dupilumab and placebo (53.5% vs 55.9%). Serious adverse events were infrequent (4.9% vs 4.1%), and discontinuations due to adverse events were uncommon and numerically less frequent with dupilumab than with placebo.[69]

In the phase 3 CUPID B trial that investigated patients with CSU who were refractory to 3 months of omalizumab therapy, a nominally significant reduction in UAS7 from baseline compared with placebo (−14.4 vs −8.5; P =0.0390) was observed at week 24. However, the primary endpoint was not achieved as no statistically significant differences were observed between groups in Itch Severity Score over 7 days (ISS7).[70]

Dupilumab has recently received approval for the treatment of CSU in several countries, where it is indicated for patients aged 2 years and older. Following approval and updated guideline recommendations, real-world evidence is expected from observational studies and registries.[1,71]

Zhu et al reported that 33 patients with CSU were treated with omalizumab, of whom 30.3% were non-responders. Among these omalizumab-refractory patients, 7 required additional therapy after also failing CsA and were subsequently treated with dupilumab; all 7 (100%) achieved complete response (UAS7 = 0) within 1–6 months. These findings suggest that dupilumab may represent an effective alternative for patients with CSU refractory to omalizumab.[72]

BTK Inhibitors: Blocking Mast Cell and Basophil Activation

Bruton's tyrosine kinase (BTK) is a key non-receptor tyrosine kinase involved in FcεRI-mediated activation of mast cells and basophils and in B-cell receptor (BCR) signaling. Dysregulation of these pathways contributes to the development of allergic and autoimmune diseases, including CSU. First, BTK inhibition reduces effector cell activation by blocking FcεRI-dependent signaling in mast cells and basophils, preventing intracellular calcium influx and the subsequent release of inflammatory mediators. Second, it disrupts BCR signaling, leading to decreased production of pathogenic IgG autoantibodies involved in autoimmune forms of CSU.[73,74] By modulating mast cells, basophils, and B cells, BTK inhibition may provide rapid symptom control, with clinical data suggesting faster suppression of histamine release and basophil activation compared with IgE-targeting therapies such as omalizumab.[75]

Second-generation BTK inhibitors (Table 3) offer improved selectivity and tolerability. Remibrutinib is a highly selective, irreversible BTK inhibitor with a short half-life and has demonstrated rapid symptom control and a favorable safety profile in clinical trials involving patients with CSU. Fenebrutinib, a reversible BTK inhibitor with strong selectivity and a moderate half-life, is currently under investigation for autoimmune diseases, including CSU. Similarly, rilzabrutinib, a reversible and orally bioavailable BTK inhibitor, has been evaluated in immune-mediated disorders such as pemphigus and CSU.[76–78]

REMIX-1 and REMIX-2 were pivotal phase 3, randomized, double-blind, placebo-controlled trials evaluating the efficacy and safety of remibrutinib in adults with CSU inadequately controlled by sgH1AH.[79] Remibrutinib demonstrated significant and clinically meaningful reductions in disease activity compared with placebo at Week 12 in both trials ($P < 0.001$), with parallel improvements in itch and hives severity scores. Symptom improvement was observed as early as Week 1. At Week 12, approximately half of remibrutinib-treated patients achieved well-controlled disease (UAS7 ≤6),

Table 3 Comparison of BTK Inhibitors for the Treatment of CSU

Drug	Binding Type	Selectivity	Half-Life	Clinical Indication	Key Safety Notes
Remibrutinib	Irreversible	High	Short	CSU, CIndU, food allergy, hidradenitis suppurativa	Mild infections
Fenebrutinib	Reversible	High	Moderate	Autoimmune diseases, CSU	Gastrointestinal symptoms, mild infections
Rilzabrutinib	Reversible	High	Moderate	Pemphigus, CSU	Mild infections

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria.

and around 30% achieved complete response (UAS7 = 0). These response rates further increased through Week 52 (UAS7≤6 in 62%), confirming sustained efficacy over long-term treatment. Remibrutinib also improved daily activity interference and sleep impairment. Benefits were consistent across prespecified subgroups, including patients with prior omalizumab exposure and low baseline IgE levels, suggesting robust efficacy across diverse clinical phenotypes.[80]

Serious adverse events were infrequent, occurring in 3.3% of patients receiving remibrutinib and 2.3% of those receiving placebo. No serious adverse event was reported in more than one patient, and none were considered by investigators to be related to the study treatment. Adverse events occurring more frequently in the remibrutinib group compared with placebo included nasopharyngitis (9.1% vs 4.9%), upper respiratory tract infections (5.7% vs 2.0%), and petechiae (4.0% vs 0.3%). Rates of treatment discontinuation due to adverse events were similar between groups, and no deaths were reported during the study period.[79,81] Overall, the REMIX trials support remibrutinib as an effective, rapidly acting, and well-tolerated therapeutic option for patients with sgH1AH-refractory CSU.

Currently, indirect comparisons from network meta-analyses suggest that remibrutinib and omalizumab have comparable efficacy and safety profiles. Notably, remibrutinib demonstrated clinical benefit in patients who had previously not responded to omalizumab, likely due to its distinct mechanism of action targeting BTK. This feature is particularly relevant for patients with autoimmune CSU, a population in which omalizumab may be less effective.[82,83]

Further research is needed to identify predictors of remibrutinib response, which could improve patient selection and optimize outcomes. Long-term studies are also warranted to assess the durability of response and extended safety profile, providing insight into sustained efficacy and tolerability over prolonged treatment periods.

Anti-KIT Antibodies: Mast Cell Depletion

KIT regulates mast cell development, survival, and activation through its interaction with stem cell factor (SCF). Mast cells maintain high KIT expression throughout their lifespan, and SCF-induced KIT dimerization triggers tyrosine kinase activation and downstream signaling pathways that promote proliferation, maturation, chemotaxis, adhesion, survival, and, at higher levels of stimulation, mediator release.[84]

Barzolvolimab

Barzolvolimab (CDX-0159) is an IgG1 monoclonal antibody directed against KIT, a receptor tyrosine kinase essential for mast cell development, survival, and activation. By blocking the interaction between KIT and its ligand, SCF, barzolvolimab inhibits downstream signaling pathways critical for mast cell maintenance. KIT inhibition may reduce mast cell numbers and activity, thereby attenuating wheal formation, angioedema, and pruritus.[7]

In a phase 1b trial of sgH1AH-refractory moderate-to-severe CSU, barzolvolimab demonstrated rapid and sustained clinical efficacy, with symptom improvement observed within 1 week and maintained through Week 24. By Week 12, 71% of barzolvolimab-treated patients achieved well-controlled disease (UAS7 ≤6) and 57% achieved complete response (UAS7 = 0), compared with 30% and 20% in the placebo group, respectively. Overall, 44% of patients had prior biologic exposure, and responses were similar in those with and without previous omalizumab use, including patients who had discontinued omalizumab due to lack of efficacy.[85]

The most common treatment-emergent adverse event with barzolvolimab was hair color change, occurring in 26% of treated patients; this was mild and reversible, with seven of nine cases resolving by the end of the study. Mild-to-moderate neutropenia occurred in 14% of patients, was not associated with increased infections, and resolved during the study.[85]

In a Phase 2 trial involving patients with CSU refractory to sgH1AH, barzolvolimab was administered at doses of 75 mg every 4 weeks, 150 mg every 4 weeks, and 300 mg every 8 weeks. At week 12, treatment with the 150 mg and 300 mg regimens resulted in statistically significant reductions in UAS7 compared with placebo.[86] In a separate 52-week phase 2 study, barzolvolimab demonstrated a rapid onset of action, with marked improvements in UAS7 observed as early as week 1. At week 52, 87.1% of patients had complete disease control. These responses were sustained over time and were consistent irrespective of previous omalizumab exposure. Notably, both disease activity scores and HR-QoL measures remained improved in 50% of patients for up to 28 weeks following the final dose, suggesting prolonged effects and possible disease modification.[87]

Briquilimab

Briquilimab is another subcutaneously administered monoclonal antibody targeting KIT that is currently being evaluated in the ongoing BEACON phase 1b/2 study in patients with CSU. Preliminary results show favorable efficacy signals, with substantial mean reductions in UAS7 at week 12 for the 120 mg and 180 mg doses administered every 8 weeks.[70]

Cyclosporine A (CsA): An Established Third-Line Option in CSU

CsA selectively inhibits calcineurin-dependent T-cell activation and proliferation. It also inhibits primed T-cells, preventing the activation of autoreactive B-cells and subsequent autoantibody production.[88] CsA's anti-inflammatory effects include dose-dependent inhibition of IgE-mediated histamine release from mast cells and basophils, as well as suppression of leukotriene C4 (LTC4) synthesis.[89] In patients with CSU, CsA treatment has been shown to significantly reduce serum levels of IL-2R, IL-5, and tumor necrosis factor alpha (TNF-α), correlating with clinical improvement.[90]

In CSU studies, CsA has been used over a broad dose range, most commonly between 3 and 5 mg/kg/day. Higher doses are often avoided because of dose-related toxicity.[91] Evidence from a large systematic review and meta-analysis indicates that meaningful clinical benefit can be achieved with lower dosing strategies. In this analysis, CsA administered at low (2 to <4 mg/kg/day) and moderate (4 to 5 mg/kg/day) doses was effective, with approximately 70% of patients showing significant improvement at low doses.[92] On this basis, several authors have proposed initiating therapy at lower doses and, in selected cases, combining CsA with omalizumab to enhance efficacy while minimizing adverse effects.[93,94]

CsA response is often rapid and increases over time. Pooled data show response rates rising from approximately 50% within the first month to over 70% by 12 weeks, indicating that lack of early improvement does not necessarily predict treatment failure.[92] Additional real-world studies have reported even faster symptom relief, with the majority of patients improving within the first 2–4 weeks of therapy.[95] Similar findings have been reported in pediatric populations, where CsA at 3 mg/kg/day led to marked reductions in disease activity by one month and complete symptom resolution by two months, with sustained disease control during longer follow-up.[96,97] CsA treatment duration varies widely across studies, extending from short courses of a few weeks to continuous therapy over several years.[92] In clinical practice, many patients can be successfully treated with limited-duration courses, whereas a smaller subset requires prolonged or repeated therapy.[93]

Long-term outcomes following CsA withdrawal are generally favorable. Several studies report durable remission in the majority of patients after stopping therapy, with disease-free intervals extending over multiple years.[98] Importantly, patients who experience relapse often respond quickly and completely to reintroduction of CsA, supporting the feasibility of retreatment.[97,99] However, the likelihood of relapse appears to be influenced by treatment length. Shorter courses are associated with higher relapse rates compared with extended treatment durations, suggesting that maintaining therapy beyond the initial response phase may improve long-term disease control.[100] Early relapse with recurrence of baseline disease severity has also been observed shortly after CsA discontinuation in some cohorts.[95] Thus, CsA duration should be individualized. Longer initial courses or repeat treatment cycles may be required to minimize relapse and achieve sustained remission.

CsA may cause renal impairment and hypertension, along with gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Neurological complaints including headache, tremor, and paresthesia, as well as flu-like symptoms such as myalgias and fatigue, can occur. Other possible adverse effects include hypertrichosis, gingival hyperplasia, metabolic abnormalities (hypertriglyceridemia, hypomagnesemia, hyperkalemia, and hyperbilirubinemia), and an increased risk of infections. Long-term use is also associated with a higher risk of malignancies, particularly cutaneous cancers and lymphoproliferative disorders.[101] However, in CSU studies most adverse events are mild and typically resolved after the dosage is reduced.[92]

Before starting CsA, patients should be evaluated to exclude infections or tumors, have their blood pressure checked, and review other medications for possible interactions. Baseline laboratory tests should include kidney and liver function, blood counts, electrolytes, uric acid, and lipid levels. During follow-up, patients should be reassessed every two weeks for the first 1–2 months and then monthly, with blood pressure checked at every visit. Laboratory monitoring should follow the same schedule, focusing on renal function, urinalysis, blood counts, and liver enzymes, while lipid levels can

be monitored less frequently unless abnormal.[101] The optimal timing for CsA discontinuation is unclear. Dose reduction is generally considered after at least three months of complete disease control.[102]

For CsA, gradual tapering rather than abrupt cessation is generally advised. One proposed approach involves decreasing the daily dose by 1 mg/kg at two-week intervals.[103] Alternatively, a structured stepwise regimen has been described, beginning with 3 mg/kg/day for six weeks, followed by sequential reductions to 2 mg/kg/day for three weeks and 1 mg/kg/day for one week before stopping treatment.[104] Such tapering strategies aim to preserve remission while reducing the likelihood of relapse.

Evidence from systematic analyses suggests that functional assays indicating autoreactivity—such as positive autologous serum skin tests, BHRA and BAT—are associated with better treatment outcomes.[12] In addition, elevated inflammatory markers, including plasma D-dimer and higher circulating levels of cytokines such as IL-2, IL-5, and TNF, alongside low baseline total IgE, have been linked to improved responsiveness to CsA.[98,105,106] Supporting these findings, data from a multicenter cohort demonstrated that patients responding to CsA more frequently had increased CRP levels, a positive family history of urticaria, and lower total IgE concentrations compared with non-responders.[107]

In general, CsA has a solid evidence base supporting its efficacy and acceptable safety profile in CSU patients who are refractory to—or lack access to—omalizumab. Accordingly, it is positioned as a third-line option in the most recent international guideline treatment algorithms, although important concerns remain regarding tolerability and safety in special populations and with long-term use.[1]

Other Emerging or Alternative Agents

A broad range of therapeutic strategies has been explored to target distinct molecular and cellular pathways involved in the pathophysiology of CSU. However, several approaches have yielded disappointing results. Agents directed against eosinophil-related cytokines (benralizumab and mepolizumab), thymic stromal lymphopoietin (tezepelumab), and Siglec-8 (lirentelimab) did not meet their primary efficacy endpoints in clinical trials. In addition, development of a Mas-related G protein-coupled receptor X2 (MRGPRX2) antagonist was discontinued after a phase 1b study due to concerning preclinical in vivo toxicology findings.[70] In contrast, clinical investigations evaluating Janus kinase (JAK) inhibitors are ongoing and may offer a novel therapeutic avenue for patients with CSU, including those who are refractory to omalizumab.[70]

Future Directions: The 2026 Precision Paradigm

Management of omalizumab-refractory CSU is moving from a one-size-fits-all strategy toward a personalized, endotype-driven approach.[2] With the approval of dupilumab and remibrutinib by international agencies and the positive results from barzolvolimab studies, the clinician's role is now to identify the "dominant driver" early, using biomarkers to identify specific endotypes. These targeted therapies may also advance biomarker development and disease-modifying strategies. The latest version of the international guidelines recommends omalizumab, dupilumab, and remibrutinib as second-line treatment options for patients with CSU refractory to sgH1AH, with the possibility of switching between these agents in cases of inadequate response before proceeding to CsA.[1] Ongoing Phase III trials with barzolvolimab are expected to provide important data, likely confirming the efficacy observed in Phase II studies. These developments support maintaining guidelines as a "living" document, as barzolvolimab may soon warrant inclusion among second-line therapeutic options. Real-world practice must identify which patients benefit most from each treatment. More precise initial treatment selection may reduce apparent anti-IgE non-response. Key differences among dupilumab, remibrutinib, and barzolvolimab are summarized in Table 4. Treatment selection should consider:

1. Route of administration: Biologics such as omalizumab, dupilumab, and anti-KIT antibodies are administered subcutaneously every 2–8 weeks. In contrast, remibrutinib is orally administered on a daily basis, but requires consistent adherence.

2. Onset of action: Remibrutinib provides rapid symptom relief, useful when early control is needed. However, fast responses are also observed in a substantial proportion of patients treated with omalizumab and barzolvolimab, and less frequently with dupilumab. Conversely, patients classified as late responders to omalizumab (after approximately 2–5 months of treatment) may require dose escalation or switching to another second-line agent. Finally, the potential for sustained disease control and possible disease modification should also be considered when selecting a long-term therapeutic strategy.

Table 4 Comparative Overview of Dupilumab, Remibrutinib, and Barzolvolimab in CSU

Feature	Dupilumab	Remibrutinib	Barzolvolimab
Target/mechanism	Blocks IL-4Rα → inhibits IL-4/IL-13 signaling (type 2 inflammation)	BTK inhibitor → blocks downstream FcεRI signaling in mast cells/basophils and BCR signaling in B cells	Anti-KIT antibody → reduces mast cell survival/function ("mast cell–depleting/impairing" strategy)
Route	Subcutaneous	Oral	Subcutaneous
Posology (typical in CSU trials/clinical use)	Loading dose then q2w	25 mg BID in phase 3 CSU trials	Investigational regimens; commonly q4w or q8w depending on dose/study
Onset of action	Usually weeks (often slower than BTK/anti-KIT)	Rapid, clinically meaningful improvement as early as week 1	Reported rapid improvements (often ~1 week in early studies)
Potential for disease modification *(conceptual)*	Possible (immunomodulation of type 2 pathways), but true modification/remission after discontinuation not established	Possible/uncertain (affects effector signaling ± autoantibody pathways), durable remission after stopping not established	High theoretical potential (mast cell targeting/depletion may outlast dosing), but not proven
Regulatory status in CSU	Approved in several countries	Approved/under review in some regions; robust phase 3 CSU data	Investigational (phase 2 positive; phase 3 ongoing)

Abbreviations: BCR, B-cell receptor; BID, twice daily; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; FcεRI, high-affinity IgE receptor; IgE, immunoglobulin E; IL-4, interleukin-4; IL-13, interleukin-13; IL-4Rα, interleukin-4 receptor alpha; KIT, stem cell factor receptor; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks.

3. Treatment history and comorbidities: Prior response to therapy and underlying endotype should guide selection. In patients refractory to omalizumab, particularly those with features suggestive of type IIb autoimmune CSU (eg, low IgE, autoimmune markers), anti-KIT therapies and BTK inhibitors may represent rational options. In contrast, patients with a type I autoallergic profile or concomitant atopic diseases (such as asthma, allergic rhinitis, or atopic dermatitis) may particularly benefit from dupilumab. Chronic inducible urticaria (CIndU) and other comorbidities should also be considered.

Conclusion

Although omalizumab remains a highly effective therapy for most patients with CSU, some continue to have inadequate disease control. In these patients, true refractoriness should be confirmed using validated PROMs, assessment of adherence and dosing, and reconsideration of differential diagnoses or CIndU. Post-omalizumab treatment should then be individualized according to response pattern, endotype features, comorbidities, safety, access, route of administration, and patient preference. CsA remains an established option, while dupilumab, BTK inhibitors, and anti-KIT antibodies offer mechanistically distinct alternatives. However, validated predictive biomarkers, comparative effectiveness data, long-term safety evidence, and standardized switching algorithms are still needed to support precision-based care.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

L. F. Ensina: Conceptualization; Literature search and interpretation; Writing - original draft; Writing - review and editing. M. Ferrer: Conceptualization; Literature search and interpretation; Writing - original draft; Writing - review and editing. M. Al-Ahmad: Conceptualization; Literature search and interpretation; Writing - original draft; Writing - review and editing. D. Fomina: Conceptualization; Literature search and interpretation; Writing - original draft; Writing - review and editing. E. Kocatürk: Conceptualization; Literature search and interpretation; Writing - original draft; Writing -

review and editing. M. Bizjak-Suran: Conceptualization; Literature search and interpretation; Writing - original draft; Writing - review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding was received for this study.

Disclosure

Dr. Luis Felipe Ensina has served as a speaker for Novartis, Sanofi, Celldex, and AbbVie, and as an advisor for Lilly, and reports personal fees from Novartis, Sanofi, Celldex, AbbVie, and Lilly, outside the submitted work.

Prof. Dr. Emek Kocatürk reports personal fees from Novartis, Sanofi, Menarini, during the conduct of the study.Dr. Marta Ferrer has received research funding from the Carlos III Health Institute (ISCIII), Novartis, GSK, and Thematic Networks for Cooperative Research Centres, and reports honoraria for advisory board and speaker bureau participation from FAES, Genentech, Menarini, MSD, Novartis, Pfizer, Regeneron, Sanofi, and Uriach. Professor Mojca Bizjak-Suran has served as a speaker and advisor for Novartis and Swixx BioPharma, and reports personal fees from these companies outside the submitted work. All other authors declare that they have no competing interests.

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