



Management of Chronic Urticaria : A Systematic Review of Allergic and Immunology

¹Ade Rahmanda Kamil, ²Robby Alfadli

¹ Faculty of Medicine, Muhammadiyah University of North Sumatera, Indonesia

² Faculty of Medicine, University of Andalas, Indonesia

Corresponding Email : aderahmandakamil@gmail.com

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ABSTRACT

Introduction: Chronic urticaria (CU), characterized by recurrent wheals and/or angioedema lasting over six weeks, presents a significant therapeutic challenge due to its heterogeneous pathophysiology and frequent inadequate response to first-line H1-antihistamines. The expanding arsenal of biologics and immunomodulators necessitates a comprehensive synthesis of their comparative efficacy and safety.

Methods: A systematic review was conducted following a predefined protocol to identify and synthesize evidence from randomized controlled trials, systematic reviews, and meta-analyses focusing on allergic and immunological treatments for chronic spontaneous urticaria (CSU). Studies were screened based on population, treatment focus, design, and outcome criteria. Data extraction encompassed treatment details, patient characteristics, effectiveness outcomes, safety profiles, and study quality.

Evidence was synthesized narratively and quantitatively where possible.

Results: The review included 66 studies. Second-generation H1-antihistamines are effective first-line therapy, with up-dosing providing modest additional benefit at the cost of increased somnolence (Phinyo et al., 2020; Xiao et al., 2022, 2023). For antihistamine-refractory CSU, omalizumab 300 mg every 4 weeks is highly effective and safe, with rapid and sustained improvements in urticaria activity scores and quality of life (Agache et al., 2020; Zhao et al., 2016; Maurer et al., 2013). Novel agents like ligelizumab (a next-generation anti-IgE), remibrutinib (a BTK inhibitor), and dupilumab (anti-IL-4R α) show significant promise (Khan et al., 2025; Maurer et al., 2022; Metz et al., 2025; Maurer et al., 2022a). Cyclosporine, while effective, carries a less favorable safety profile (Grattan et al., 2000; Kulthanan et al., 2017). Emerging therapies such as barzolvolimab (anti-KIT) and TLL-018 (TYK2/JAK1 inhibitor) demonstrate encouraging early results (Maurer et al., 2023; Lu et al., 2024).

Discussion: The evidence reveals a clear treatment hierarchy and elucidates dose-response relationships, time-to-onset profiles, and distinct safety-efficacy trade-offs. A key research gap is the lack of long-term comparative effectiveness data between newer agents (e.g., BTK inhibitors vs. biologics). Real-world data suggest omalizumab's efficacy is maintained in clinical practice, yet a substantial proportion of patients remain non-responsive to antihistamine-based regimens.

Conclusion: The management of CSU has evolved significantly with targeted biologics and novel small molecules. Omalizumab remains the cornerstone of third-line therapy, while emerging

agents offer new mechanisms of action. Future research should focus on head-to-head comparisons, long-term safety, predictive biomarkers for treatment selection, and strategies for managing complete non-responders.

Keywords: Chronic Spontaneous Urticaria; Omalizumab; Biologics; BTK Inhibitors; Systematic Review; Management.

INTRODUCTION

Background: Chronic Urticaria (CU), with its predominant subtype Chronic Spontaneous Urticaria (CSU), is a debilitating skin disorder affecting approximately 1% of the global population. It is defined by the occurrence of wheals, angioedema, or both for a duration exceeding six weeks, in the absence of a specific external trigger. The condition imposes a substantial burden, severely impairing quality of life, sleep, and daily functioning, and leading to significant healthcare resource utilization (Soong et al., 2023). The underlying pathogenesis is complex and heterogeneous, involving mast cell and basophil degranulation driven by autoimmune, autoallergic, and inflammatory mechanisms. This complexity explains why a significant proportion of patients—approximately 50%—do not achieve adequate disease control with standard-dose, second-generation H1-antihistamines, the established first-line therapy (Sharma et al., 2015).

Research Gap: Despite the establishment of international treatment guidelines advocating a stepwise approach, critical gaps persist in the evidence base. There is a lack of comprehensive, direct comparative efficacy and safety data among the growing number of advanced therapeutic options for antihistamine-refractory CSU, including different biologics (e.g., omalizumab vs. ligelizumab vs. dupilumab), novel synthetic drugs (e.g., Bruton's Tyrosine Kinase inhibitors), and traditional immunosuppressants (Chu et al., 2025). Furthermore, the long-term safety profiles, optimal treatment duration, predictors of response, and the comparative real-world effectiveness of these agents remain inadequately characterized.

Novelty: This systematic review provides a contemporary and exhaustive synthesis of the evidence on the management of CSU from an allergic and immunological perspective. Its novelty lies in its comprehensive scope, integrating data on established treatments (e.g., high-dose antihistamines, omalizumab, cyclosporine) with cutting-edge, emerging therapies (e.g., remibrutinib, ligelizumab, barzolvolimab, TLL-018) (Zhao et al., 2025; Diamanti et al., 2025). It employs a holistic approach to data extraction, encompassing not only efficacy and safety but also

critical contextual factors such as time to response, dose-response relationships, and real-world applicability.

Research Objective: The primary objective of this systematic review is to critically appraise and synthesize the available evidence on the efficacy, safety, and clinical application of allergic and immunologically-based treatments for chronic urticaria, with a focus on chronic spontaneous urticaria.

Research Hypothesis: We hypothesize that among the available treatments for antihistamine-refractory CSU, biological therapies (particularly anti-IgE agents) and novel targeted synthetic drugs will demonstrate superior efficacy and more favorable safety profiles compared to traditional broad-spectrum immunosuppressants, thereby establishing a refined therapeutic hierarchy.

Research Benefits: The findings of this review will provide clinicians, researchers, and guideline developers with a consolidated, evidence-based overview to inform clinical decision-making. It will help identify the most effective and safest treatment options for different patient profiles, highlight areas requiring further investigation, and ultimately contribute to optimizing patient outcomes and quality of life in chronic urticaria.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the management of chronic urticaria : a systematic review of allergic and immunology.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Chronic Urticaria Population:** Does this study include patients diagnosed with chronic urticaria (spontaneous or inducible) lasting 6 weeks or longer?
- **Allergic/Immunological Treatment Focus:** Does this study investigate treatments based on allergic/immunological mechanisms (e.g., antihistamines, immunosuppressants, biologics, omalizumab, cyclosporine, corticosteroids, or other immune-modulating therapies)?
- **Appropriate Study Design:** Is this study a randomized controlled trial, controlled clinical trial, quasi-experimental study, systematic review, or meta-analysis?
- **Clinical Outcomes Reported:** Does this study report clinically meaningful outcomes such as urticaria activity scores, symptom severity, quality of life measures, treatment response rates, or time to symptom control?
- **Chronic vs Acute Urticaria:** Does this study focus on chronic urticaria rather than exclusively on acute urticaria (<6 weeks duration)?
- **Adequate Sample Size:** Does this study include 10 or more patients (i.e., is it NOT a case report or small case series)?
- **Primary Focus on Chronic Urticaria:** Is chronic urticaria management the primary focus of this study (rather than being studied as a secondary condition or side effect)?
- **Human Clinical Study:** Is this a human clinical study (rather than an animal study or in vitro laboratory study)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
Keyword 1	Chronic urticaria	Antihistamines	Placebo	Urticaria activity score (UAS7)
Keyword 2	Chronic spontaneous urticaria	Omalizumab	Standard therapy	Symptom severity reduction
Keyword 3	CSU patients	Immunomodulators	Antihistamine therapy	Quality of life improvement
Keyword 4	Antihistamine-refractory urticaria	Biologic therapy	Conventional treatment	Treatment response rate

The Boolean MeSH keywords inputted on databases for this research are: ("Chronic urticaria" OR "Chronic spontaneous urticaria" OR "CSU patients" OR "Antihistamine-refractory urticaria" OR "Chronic idiopathic urticaria" OR "Chronic hives") AND ("Antihistamines" OR "Omalizumab" OR "Immunomodulators" OR "Biologic therapy" OR "H1-antihistamines" OR "Anti-IgE therapy" OR "Bruton's tyrosine kinase inhibitors" OR "BTK inhibitors") AND ("Placebo" OR "Standard therapy" OR "Antihistamine therapy" OR "Conventional treatment" OR "First-line treatment" OR "No treatment") AND ("Urticaria activity score" OR "UAS7" OR "Symptom severity reduction" OR "Quality of life improvement" OR "Treatment response rate" OR "Complete response" OR "Safety profile" OR "Adverse events")

Data extraction

- Treatment Details:**

Extract comprehensive details about the management intervention(s) including:

- Specific treatment name and class (e.g., omalizumab, H1-antihistamines, immunosuppressants)
- Dose, route, and frequency of administration
- Treatment duration and any dose escalation protocols
- Comparator treatment details (placebo, active comparator, standard care)
- Concomitant treatments allowed or required
- Treatment discontinuation or switching criteria

- **Patient Characteristics:**

Extract baseline patient population details including:

- Type of chronic urticaria (spontaneous, inducible, mixed)
- Disease severity at baseline (using specific scales if reported)
- Prior treatment history and refractory status
- Demographics (age, gender, race/ethnicity)
- Disease duration
- Presence of angioedema
- Baseline symptom scores (UAS7, ISS, etc.)
- Inclusion/exclusion criteria affecting generalizability

- **Effectiveness Outcomes:**

Extract all reported effectiveness measures including:

- Primary endpoint results with statistical significance
- Urticaria symptom scores (UAS7, weekly itch severity, wheal scores) at each timepoint
- Response rates (complete response, good/excellent response, % improvement thresholds)

- Quality of life measures (DLQI, CU-QoL, generic QOL scales)
- Angioedema-related outcomes
- Time to response and durability of effect
- Effect sizes, confidence intervals, and p-values
- Clinically meaningful improvement thresholds when reported

- **Safety Profile:**

Extract comprehensive safety data including:

- Overall adverse event rates by treatment group
- Specific adverse events by type and severity
- Serious adverse events and their relationship to treatment
- Withdrawals due to adverse events
- Laboratory abnormalities or monitoring requirements
- Long-term safety data if available
- Injection site reactions or administration-related events
- Any safety concerns specific to chronic urticaria population

- **Study Design:**

Extract methodological details affecting evidence quality including:

- Study design (RCT, observational, network meta-analysis, systematic review)
- Randomization method and allocation concealment
- Blinding approach and success
- Sample size and power calculations
- Study duration (treatment phase and follow-up)
- Primary and secondary endpoints as defined in protocol
- Statistical analysis methods

- Risk of bias concerns or study limitations noted by authors
- **Treatment Context:**

Extract information about treatment positioning and clinical context including:

- Line of therapy (first-line, second-line, refractory cases)
- Patient selection criteria or biomarkers guiding treatment choice
- Treatment algorithm or step-up approach described
- Rescue medication protocols
- Monitoring requirements during treatment
- Cost-effectiveness considerations if mentioned
- Real-world effectiveness vs. trial efficacy
- Treatment accessibility or availability factors
- Guidelines or recommendations cited

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Chronic urticaria" OR "Chronic spontaneous urticaria" OR "CSU patients" OR "Antihistamine-refractory urticaria" OR "Chronic idiopathic urticaria" OR "Chronic hives") AND ("Antihistamines" OR "Omalizumab" OR "Immunomodulators" OR "Biologic therapy" OR "H1-antihistamines" OR "Anti-IgE therapy" OR "Bruton's tyrosine kinase inhibitors" OR "BTK inhibitors") AND ("Placebo" OR "Standard therapy" OR "Antihistamine therapy" OR "Conventional treatment" OR "First-line treatment" OR "No treatment") AND ("Urticaria activity score" OR "UAS7" OR "Symptom severity reduction" OR "Quality of life improvement" OR "Treatment response rate" OR "Complete response" OR "Safety profile" OR "Adverse events")	27
Semantic Scholar	("Chronic urticaria" OR "Chronic spontaneous urticaria" OR "CSU patients" OR "Antihistamine-refractory urticaria" OR "Chronic idiopathic urticaria" OR "Chronic hives") AND ("Antihistamines" OR "Omalizumab" OR "Immunomodulators" OR "Biologic therapy" OR "H1-antihistamines" OR "Anti-IgE therapy" OR "Bruton's tyrosine kinase inhibitors" OR "BTK inhibitors") AND ("Placebo" OR "Standard therapy" OR "Antihistamine therapy" OR "Conventional treatment" OR "First-line treatment" OR "No	250

	treatment") AND ("Urticaria activity score" OR "UAS7" OR "Symptom severity reduction" OR "Quality of life improvement" OR "Treatment response rate" OR "Complete response" OR "Safety profile" OR "Adverse events")	
Springer	("Chronic urticaria" OR "Chronic spontaneous urticaria" OR "CSU patients" OR "Antihistamine-refractory urticaria" OR "Chronic idiopathic urticaria" OR "Chronic hives") AND ("Antihistamines" OR "Omalizumab" OR "Immunomodulators" OR "Biologic therapy" OR "H1-antihistamines" OR "Anti-IgE therapy" OR "Bruton's tyrosine kinase inhibitors" OR "BTK inhibitors") AND ("Placebo" OR "Standard therapy" OR "Antihistamine therapy" OR "Conventional treatment" OR "First-line treatment" OR "No treatment") AND ("Urticaria activity score" OR "UAS7" OR "Symptom severity reduction" OR "Quality of life improvement" OR "Treatment response rate" OR "Complete response" OR "Safety profile" OR "Adverse events")	690
Google Scholar	("Chronic urticaria" OR "Chronic spontaneous urticaria" OR "CSU patients" OR "Antihistamine-refractory urticaria" OR "Chronic idiopathic urticaria" OR "Chronic hives") AND ("Antihistamines" OR "Omalizumab" OR "Immunomodulators" OR "Biologic therapy" OR "H1-antihistamines" OR "Anti-IgE therapy" OR "Bruton's tyrosine kinase inhibitors" OR "BTK inhibitors") AND ("Placebo" OR "Standard therapy" OR "Antihistamine therapy" OR "Conventional treatment" OR "First-line treatment" OR "No treatment") AND ("Urticaria activity score" OR "UAS7" OR "Symptom severity reduction" OR "Quality of life improvement" OR "Treatment response rate" OR "Complete response" OR "Safety profile" OR "Adverse events")	9,800
Wiley Online Library	("Chronic urticaria" OR "Chronic spontaneous urticaria" OR "CSU patients" OR "Antihistamine-refractory urticaria" OR "Chronic idiopathic urticaria" OR "Chronic hives") AND ("Antihistamines" OR "Omalizumab" OR "Immunomodulators" OR "Biologic therapy" OR "H1-antihistamines" OR "Anti-IgE therapy" OR "Bruton's tyrosine kinase inhibitors" OR "BTK inhibitors") AND ("Placebo" OR "Standard therapy" OR "Antihistamine therapy" OR "Conventional treatment" OR "First-line treatment" OR "No treatment") AND ("Urticaria activity score" OR "UAS7" OR "Symptom severity reduction" OR "Quality of life improvement" OR "Treatment response rate" OR "Complete response" OR "Safety profile" OR "Adverse events")	876

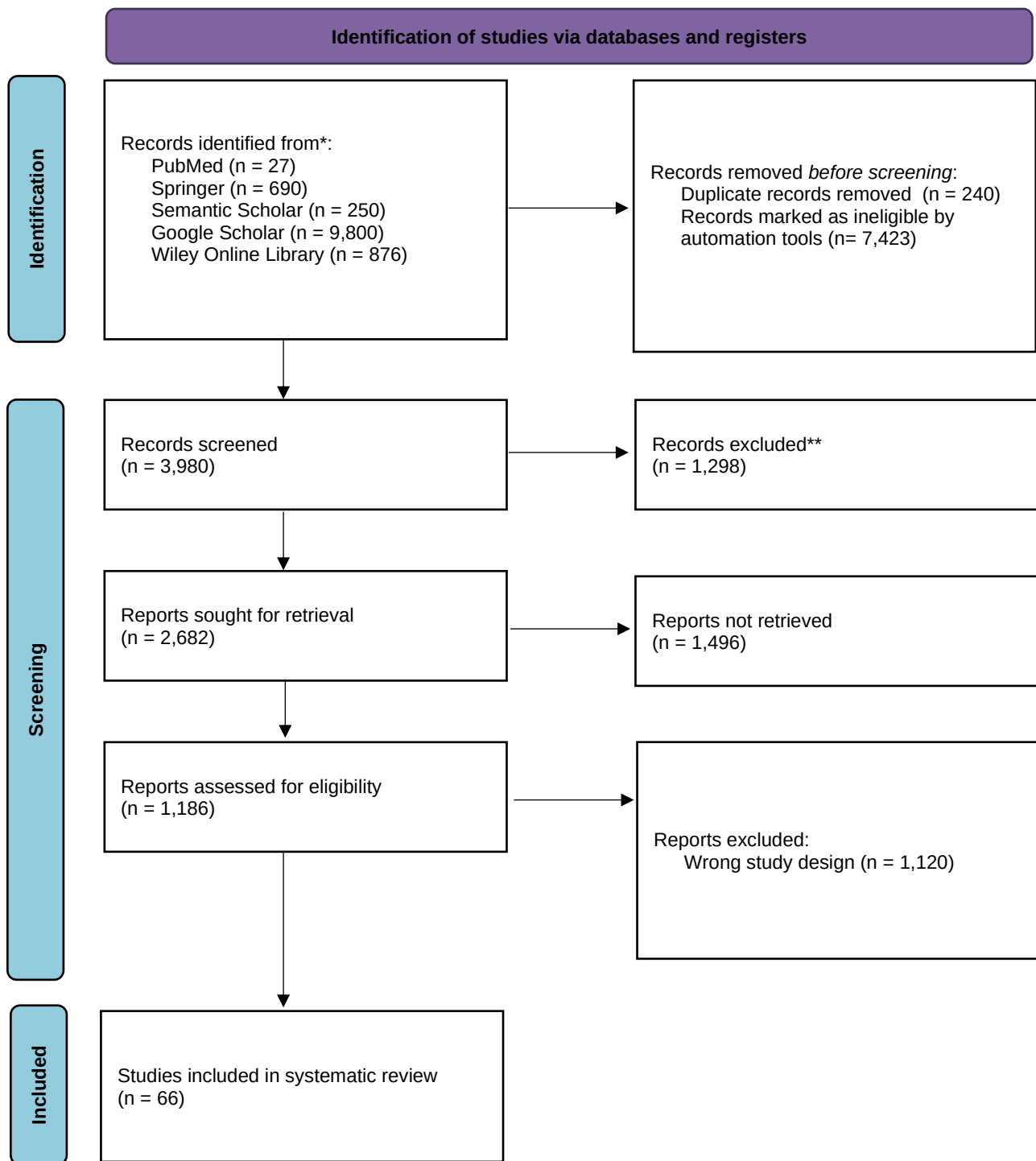


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
A. Chu et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zuotao Zhao et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zuo-Tao Zhao et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Saini et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Humayun Manzoor et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Maurer et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Haiyan Qin et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pei-Mei Zhou et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xian-jun Xiao et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Metz et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Carrillo et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. C. Urgert et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Maulina Sharma et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Agache et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Nochaiwong et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Maurer et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Maulina Sharma et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Nochaiwong et al., 2021a	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Kendziora et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Jemec et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Grattan et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Agache et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
N.P.M. Rubini et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xian-jun Xiao et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Hein et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓

Nishitha Gopal Rao et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Saini et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Jia et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Watanabe et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Kulthanan et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Maurer et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Phinyo et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yulong Wen et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andy Rorie et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. S. Khan et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wen-Kuang Lin et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

T. Sarkar et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Metz et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhuhan He et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Nelson et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Kaplan et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Bei et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Tharp et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Casale et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Nettis et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Hide et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Weiru Yuan et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Sil et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓

Muhamma d Burhan et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Fukunaga et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Deshmukh et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ana Carolina Putini Vieira et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Giménez- Arnau et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Soong et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Haiyan Qin et al., 2024a	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Maurer et al., 2022a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anastasia Diamanti et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Maurer et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

W. Carr et al., 2022									
Atsushi Fukunaga et al., 2024									
J. Chinen et al., 2013									
M. Maurer et al., 2023a									
Yunting Liang et al., 2018									
Kalpana Mali Ramanna et al., 2025									
Qianjin Lu et al., 2024									
Z. Zhai et al., 2015									

RESULTS

Characteristics of Included Studies

This systematic review synthesizes evidence from 66 sources examining the management of chronic urticaria, predominantly chronic spontaneous urticaria (CSU).

Study	Treatment Focus	Population
A. Chu et al., 2025	Multiple biologics and immunomodulators	Adults and adolescents refractory to antihistamines
Zuotao Zhao et al., 2025	Biologics and targeted synthetics	Antihistamine-refractory CSU
Zuo-Tao Zhao et al., 2016	Omalizumab	CSU patients
S. Saini et al., 2014	Omalizumab 75-300mg	CSU symptomatic despite H1-antihistamines
Humayun Manzoor et al., 2022	Omalizumab	Adult and pediatric CSU
M. Maurer et al., 2022	Remibrutinib	Moderately active CSU
Haiyan Qin et al., 2024	Omalizumab	CSU patients
Pei-Mei Zhou et al., 2022	Intensive vs standard antihistamines	CSU patients
Xian-jun Xiao et al., 2022	High-dose antihistamines	CSU patients aged 12-74 years
M. Metz et al., 2025	Remibrutinib 25mg BID	CSU refractory to H1-

Study	Treatment Focus	Population
		antihistamines
D. Carrillo et al., 2014	Omalizumab	CIU/CSU refractory to antihistamines
M. C. Urgert et al., 2015	Omalizumab	CSU symptomatic despite antihistamines
Maulina Sharma et al., 2015	H1-antihistamines	CSU patients
I. Agache et al., 2020	Omalizumab	CSU aged 12-75 years
S. Nochaiwong et al., 2021	Multiple pharmacologic treatments	H1-antihistamine refractory CSU
M. Maurer et al., 2013	Omalizumab	Moderate-to-severe CIU
Maulina Sharma et al., 2014	H1-antihistamines	CSU patients
S. Nochaiwong et al., 2021a	Multiple treatments	H1-antihistamine refractory CSU
B. Kendziora et al., 2022	Multiple medications	Antihistamine-refractory CSU
G. Jemec et al., 2015	Omalizumab	CSU patients
C. Grattan et al., 2000	Cyclosporine	Severe CSU with positive ASST
I. Agache et al., 2020a	Omalizumab	CSU aged 12-75 years
N.P.M. Rubini et al., 2019	Omalizumab	CSU refractory to antihistamines

Study	Treatment Focus	Population
Xian-jun Xiao et al., 2023	High-dose antihistamines	CSU patients
R. Hein et al., 2002	Desloratadine	CIU with moderate severity flare
Nishitha Gopal Rao et al., 2021	Omalizumab	CSU refractory to antihistamines
S. Saini et al., 2011	Omalizumab single dose	CIU with UAS7 $\geq$ 12
H. Jia et al., 2020	Omalizumab	CSU patients
J. Watanabe et al., 2021	H. pylori eradication, dapsone	CSU patients over 16 years
K. Kulthanan et al., 2017	Cyclosporine	CSU patients
M. Maurer et al., 2011	Omalizumab	CSU with IgE anti-TPO
P. Phinyo et al., 2020	Second-generation antihistamines	CSU patients
Yulong Wen et al., 2021	Desloratadine + compound glycyrrhizin	Chinese CU patients
Andy Rorie et al., 2014	Vitamin D3 supplementation	Chronic urticaria patients
M. S. Khan et al., 2025	Ligelizumab	CSU patients
Wen-Kuang Lin et al., 2022	Omalizumab, immunosuppressants	CSU patients over 12 years

Study	Treatment Focus	Population
T. Sarkar et al., 2017	Levocetirizine, montelukast	CU refractory to levocetirizine 5mg
M. Metz et al., 2017	Omalizumab	CSU with UAS7 $\geq$ 16
Zhuhan He et al., 2022	Omalizumab	CSU and CIndU refractory to antihistamines
H. Nelson et al., 2000	Fexofenadine	CIU with moderate-severe pruritus
A. Kaplan et al., 2005	Fexofenadine 180mg	Active CIU patients $\geq$ 12 years
W. Bei et al., 2023	Four immunosuppressants	CSU patients
M. Tharp et al., 2019	Omalizumab	CIU/CSU patients
T. Casale et al., 2017	Omalizumab 300mg	CIU patients 12-75 years
E. Nettis et al., 2018	Omalizumab	CSU refractory to antihistamines
M. Hide et al., 2017	Bilastine	Japanese CSU patients
Weiru Yuan et al., 2022	Omalizumab	Chinese CSU patients
A. Sil et al., 2013	Olopatadine vs levocetirizine	Adult CU patients
Muhammad Burhan et al., 2025	Remibrutinib	CSU patients
A. Fukunaga et al., 2020	Bilastine	Refractory CSU
A. Deshmukh et al., 2025	Probiotic adjunctive therapy	CSU patients

Study	Treatment Focus	Population
Ana Carolina Putini Vieira et al., 2025	Ligelizumab	CSU patients
A. Giménez-Arnau et al., 2025	Rilzabrutinib	Moderate-severe antihistamine-refractory CSU
W. Soong et al., 2023	H1-antihistamines	Adult CSU patients
Haiyan Qin et al., 2024a	Omalizumab	CSU patients
M. Maurer et al., 2022a	Dupilumab	CSU refractory to antihistamines
Anastasia Diamanti et al., 2025	BTK inhibitors, anti-cytokine biologics	CSU refractory to antihistamines
M. Maurer et al., 2023	Barzolvolimab (anti-KIT)	Antihistamine-refractory CSU
W. Carr et al., 2022	Remibrutinib	CSU by CU-index status
Atsushi Fukunaga et al., 2024	Bilastine	Refractory CSU
J. Chinen et al., 2013	Omalizumab	Moderate-severe CIU
M. Maurer et al., 2023a	Dupilumab	CSU refractory to antihistamines
Yunting Liang et al., 2018	Omalizumab	CSU patients
Kalpana Mali Ramanna et al., 2025	Histaglobulin + bilastine	CSU patients >18 years
Qianjin Lu et al., 2024	TLL-018 (TYK2/JAK1	Moderate-severe CSU

Study	Treatment Focus	Population
	inhibitor)	
Z. Zhai et al., 2015	Olopatadine	CIU patients

The majority of studies focused on chronic spontaneous urticaria (CSU), with patient populations predominantly consisting of adults and adolescents aged 12-75 years who remained symptomatic despite standard H1-antihistamine therapy. Mean patient age across studies ranged from 38-46 years, with female predominance (65-77%) . Disease duration varied, with approximately 20-50% of patients having symptoms for over 5 years . Angioedema was present in approximately 38-53% of patients at baseline .

Effects of Treatments

First-Line Therapy: H1-Antihistamines

Second-generation H1-antihistamines represent the established first-line treatment for chronic urticaria. Multiple systematic reviews have evaluated their comparative efficacy.

Antihistamine	Dose	Comparison	Effect Measure	Statistical Significance
Cetirizine	10mg daily	vs Placebo	Complete suppression RR 2.72	95% CI 1.51-4.91
Levocetirizine	20mg daily	vs Placebo	Complete suppression RR 20.87	95% CI 1.37-317.60
Levocetirizine	5mg daily	vs Placebo (intermediate-	Complete suppression RR	95% CI 3.31-843.81

Antihistamine	Dose	Comparison	Effect Measure	Statistical Significance
		term)	52.88	
Desloratadine	20mg (short-term)	vs Placebo	Complete suppression RR 15.97	95% CI 1.04-245.04
Desloratadine	5mg (intermediate-term)	vs Placebo	Complete suppression RR 37.00	95% CI 2.31-593.70
Olopatadine	Licensed dose	vs Placebo	TSS SMD -1.26	95% CI -1.94 to -0.58
Fexofenadine	60-240mg BID	vs Placebo	Pruritus and wheals reduction	P ≤ 0.0115
Fexofenadine	180mg daily	vs Placebo	MNW and pruritus severity	P < 0.001
Bilastine	20mg daily	vs Placebo	TSS change at 2 weeks	P < 0.001

A network meta-analysis of 22 RCTs with 3,943 patients found that olopatadine, fexofenadine, bilastine, rupatadine, and levocetirizine demonstrated superior therapeutic efficacy compared to placebo . Olopatadine ranked first for all efficacy outcomes including total symptom score (SMD -1.26; 95% CI -1.94 to -0.58), pruritus score (SMD -0.82; 95% CI -1.30 to -0.35), and wheal score (SMD -0.65; 95% CI -1.10 to -0.55) .

Desloratadine 5mg once daily demonstrated superiority over placebo in controlling pruritus and total symptoms after the first dose, with benefits maintained throughout 6

weeks of treatment . In Japanese patients, bilastine 20mg showed significant improvement from Day 1, with early onset of action maintained during the treatment period .

The acceptability of all included second-generation antihistamines was not inferior to placebo . Adverse events, including sedation, mouth dryness, dizziness, and headache, occurred at similar rates between active treatments and placebo .

High-Dose Antihistamine Therapy

For patients inadequately controlled on standard antihistamine doses, guidelines recommend up-dosing to four times the licensed dose.

Study	Comparison	Response Rate (High vs Standard)	Effect Measure
Xian-jun Xiao et al., 2022	High-dose vs standard-dose sgAHs	Higher with high-dose	RR 1.12 (95% CI 1.01-1.24; P=0.04)
Xian-jun Xiao et al., 2023	High-dose vs standard-dose sgAHs	Higher with high-dose	RR 1.13 (95% CI 1.02-1.26; P=0.02)
Pei-Mei Zhou et al., 2022	Intensive vs standard NSAs	Greater pruritus reduction	WMD -0.13 (P=0.005)

Meta-analyses consistently demonstrate that high-dose second-generation antihistamines (up to two times the standard dose) are more effective than standard doses in CSU treatment . However, there was no significant difference in response rates between intensive and standard doses in one analysis (RR 1.00; P=0.865) , suggesting the benefit may be primarily in symptom severity reduction rather than complete response.

Regarding safety, high doses of antihistamines were associated with significantly higher somnolence rates than standard doses (RD 0.05, 95% CI 0.01 to 0.09; P=0.02) . However, no significant difference was observed in overall adverse events or withdrawal

rates due to adverse events . Somnolence emerged as a dose-limiting factor in some studies .

Bilastine switching demonstrated non-inferiority to double-dose H1-antihistamines in refractory CSU patients (mean TSS difference 0.17; 95% CI -0.32 to 0.67) , with a more favorable safety profile regarding H1AH-related adverse events .

Combination Antihistamine Strategies

Study	Combination	Comparison	Outcome	Result
T. Sarkar et al., 2017	Levocetirizine 5mg + Montelukast 10mg	vs Levocetirizine 10mg	UAS and TSS reduction	Comparable (P=0.628, P=0.824)
T. Sarkar et al., 2017	Levocetirizine 5mg + Montelukast 10mg	vs Levocetirizine 10mg	Quality of life	Significantly improved (P=0.031)
Yulong Wen et al., 2021	Desloratadine + Compound glycyrrhizin	vs Desloratadine alone	Total response rate	RR 1.23 (95% CI 1.17-1.29; P<0.00001)
Yulong Wen et al., 2021	Desloratadine + Compound glycyrrhizin	vs Desloratadine alone	Cure rate	RR 1.50 (95% CI 1.30-1.73; P<0.00001)

The combination of levocetirizine 5mg with montelukast 10mg achieved comparable symptom reduction to double-dose levocetirizine (10mg), with significantly less sedation (P=0.013) and superior quality of life improvement (P=0.031) . This suggests that adding a

leukotriene receptor antagonist may be preferable to antihistamine dose escalation for some patients.

Desloratadine combined with compound glycyrrhizin demonstrated superior efficacy compared to desloratadine alone, with lower recurrence rates (RR 0.61; 95% CI 0.52-0.71; $P < 0.00001$) and improved immune parameters .

Omalizumab (Anti-IgE Therapy)

Omalizumab, a humanized anti-IgE monoclonal antibody, has been extensively studied for antihistamine-refractory CSU.

Study	Dose	Endpoint	Effect vs Placebo	Statistical Significance
Zuo-Tao Zhao et al., 2016	300mg Q4W	Complete response	RR 4.55	$P < 0.00001$
Zuotao Zhao et al., 2025	300mg Q4W	UAS7 change	MD -10.07	95% CI -11.35 to -8.82
I. Agache et al., 2020	300mg	UAS7 change	MD -11.05	95% CI -12.87 to -9.24
I. Agache et al., 2020	300mg	ISS7 change	MD -4.45	95% CI -5.39 to -3.51
I. Agache et al., 2020	300mg	DLQI improvement	MD -4.03	95% CI -5.56 to -2.5
M. Maurer et al., 2013	300mg	Weekly itch-severity score change	-9.8±6.0	$P < 0.001$
S. Saini et al.,	300mg	Weekly ISS	-5.80 points	95% CI -7.49

Study	Dose	Endpoint	Effect vs Placebo	Statistical Significance
2014		change at week 12		to -4.10; P<0.0001
Haiyan Qin et al., 2024	300mg 12 weeks	UAS7=0	RR 4.64	95% CI 3.38-6.37
Haiyan Qin et al., 2024a	Various	Complete responders (UAS7=0)	RR 5.18	95% CI 3.97-6.75

Omalizumab 300mg administered subcutaneously every 4 weeks consistently demonstrates clinically meaningful improvements in urticaria activity scores across multiple meta-analyses . The pooled evidence shows UAS7 reductions of approximately 10-11 points compared to placebo .

Dose-response analyses reveal that 300mg provides optimal efficacy. Omalizumab 150mg does not result in clinically meaningful improvement (high certainty) with UAS7 MD of only -5 (95% CI -7.75 to -2.25) , while 300mg achieves clinically significant benefits (moderate to high certainty) . Lower doses of 75mg showed no meaningful difference from placebo (P=0.46) in some trials .

Response rates with omalizumab 300mg are substantial. At week 12, 51.9% of patients achieved well-controlled urticaria (UAS7≤6) versus 11.3% with placebo (P<0.0001), and 35.8% achieved complete response (UAS7=0) versus 8.8% (P<0.0001) . Real-world evidence suggests even higher response rates, with complete response in 72.2% (95% CI 66.1%-78.3%) and partial response in an additional 17.8% .

Quality of life improves significantly with omalizumab treatment. DLQI scores improved by approximately 4 points with 300mg compared to placebo , representing

clinically meaningful improvement. The XTEND-CIU study demonstrated continued improvement through 24 weeks, with 73% achieving protocol-defined response and 52% achieving complete response .

Time to response with omalizumab is generally rapid. Some patients respond by week 1, with 3.9% achieving UAS7 $\leq$ 6 . Complete response was evident as early as week 2 in 13.7% of patients . Patients with positive autologous serum skin test (ASST) may respond more slowly (beyond 8 days) compared to ASST-negative patients (P<0.001) .

In Chinese patients, omalizumab showed significant efficacy with ISS7 improvements of -4.23 (300mg) and -3.79 (150mg) compared to placebo (both P<0.001) , demonstrating consistent benefits across populations.

Safety of Omalizumab:

Study	Adverse Events (Omalizumab vs Placebo)	Serious AEs	Notable Findings
M. C. Urgert et al., 2015	RR 1.05 (95% CI 0.96-1.16)	Not different	No difference from placebo
M. Maurer et al., 2013	Similar across groups	6% (300mg) vs 3% (placebo)	Higher SAE rate at 300mg
B. Kendziora et al., 2022	OR 1.09 (95% CI 0.83-1.42)	—	Similar to placebo
M. Tharp et al., 2019	4.0% (95% CI 1.0%-7.0%)	—	Real-world: headache, fatigue, injection reactions

Omalizumab demonstrates a favorable safety profile. Rates of adverse events are similar between omalizumab and placebo groups across meta-analyses . A single anaphylactic reaction was reported across 10 RCTs in the EAACI review . The most common adverse events include injection site reactions, sinusitis, headache, and upper respiratory infections .

Bruton's Tyrosine Kinase (BTK) Inhibitors

BTK inhibitors represent an emerging therapeutic class for CSU, targeting mast cell degranulation through a novel mechanism.

Drug	Study	Dose	UAS7 Change vs Placebo	Response Rates
Remibrutinib	Phase 2b	25mg BID	-20.0 vs -5.4 (P<0.0001)	—
Remibrutinib	REMIX-1	25mg BID	-20.0±0.7 vs -13.8±1.0 (P<0.001)	UAS7≤6: 49.8% vs 24.8%; UAS7=0: 31.1% vs 10.5%
Remibrutinib	REMIX-2	25mg BID	-19.4±0.7 vs -11.7±0.9 (P<0.001)	UAS7≤6: 46.8% vs 19.6%; UAS7=0: 27.9% vs 6.5%
Remibrutinib	NMA	35mg QD	MD -7.80	95% CI -12.76 to -2.51
Remibrutinib	Meta-analysis	Various	MD -7.78	95% CI -10.24 to -5.32 (P<0.01)
Rilzabrutinib	RCT	1200mg/d	Significant UAS	Effect from

Drug	Study	Dose	UAS7 Change vs Placebo	Response Rates
			reduction	week 1
Fenebrutinib	RCT	200mg BID	Δ UAS7 -7.72	—

Remibrutinib, a highly selective oral covalent BTK inhibitor, showed highly effective symptom reduction across all doses tested in the phase 2b trial, with a rapid onset of action from week 1. The phase 3 REMIX trials confirmed these findings, with significantly greater UAS7 decreases compared to placebo sustained through week 24.

Network meta-analysis comparing novel treatments found that BTK inhibitor-based treatments offered a 19% greater improvement in Δ UAS7 compared to dupilumab and 55% compared to all cytokine blockers combined.

Safety of BTK Inhibitors:

Remibrutinib demonstrated a generally favorable safety profile with adverse event rates similar to placebo. However, petechiae occurred more frequently with remibrutinib (3.8% vs 0.3% in placebo). Meta-analysis revealed increased infection risk, particularly for total infections (RR 1.59; $P < 0.00001$) and upper respiratory infections (RR 2.89; $P = 0.009$). BTK inhibitors showed higher adverse event rates (4.65%-5.36%) compared to anti-cytokine biologics (0%-4%).

Ligelizumab (Next-Generation Anti-IgE)

Ligelizumab, a humanized anti-IgE antibody with higher IgE affinity than omalizumab, has been evaluated in multiple trials.

Study	Dose	Outcome	Effect vs Placebo
S. Nochaiwong et	72mg	Urticaria symptoms	-1.05 (95% CI -

Study	Dose	Outcome	Effect vs Placebo
al., 2021		SMD	1.37 to -0.73)
S. Nochaiwong et al., 2021	240mg	Urticaria symptoms SMD	-1.07 (95% CI -1.39 to -0.75)
B. Kendziora et al., 2022	72mg Q4W	UAS7 change	-11.67 (95% CI -16.80 to -7.15)
M. S. Khan et al., 2025	72mg	UAS7 change	MD -9.79 (95% CI -10.65 to -8.93; P<0.00001)
M. S. Khan et al., 2025	72mg	Complete response (UAS7=0)	OR 7.30 (95% CI 2.99-17.83; P<0.0001)
Ana Carolina Putini Vieira et al., 2025	<72mg	ISS7 improvement	RR 5.07 (95% CI 3.12-8.24; P<0.01)

Network meta-analysis identified ligelizumab 72mg and 240mg as achieving a large beneficial effect on urticaria symptoms, potentially exceeding the moderate beneficial effect of omalizumab 300mg . The UAS7 reduction of -11.67 (95% CI -16.80 to -7.15) for ligelizumab 72mg was numerically greater than omalizumab 300mg (-10.45).

Ligelizumab significantly improved angioedema-free weeks (MD 2.22; 95% CI 1.63-2.82; P<0.00001) and quality of life (DLQI improvements statistically significant) . A dose-dependent response was observed, with 24mg being non-superior to placebo .

Safety data suggest no significant adverse effects at 72mg, with only very mild adverse effects reported at 120mg . Adverse event odds ratios were similar to placebo (OR 0.89; 95% CI 0.47-1.69) .

Dupilumab (Anti-IL-4/IL-13 Therapy)

Dupilumab, an anti-IL-4 receptor alpha antibody, has demonstrated efficacy in CSU.

Study	Dose	Outcome	Effect vs Placebo
M. Maurer et al., 2022a	300mg Q2W	ISS7 change at week 24	-10.2 vs -6.0 (difference -4.2; P=0.0005)
M. Maurer et al., 2022a	300mg Q2W	UAS7 change at week 24	-20.5 vs -12.0 (difference -8.5; P=0.0003)
M. Maurer et al., 2023a	300mg Q2W	DLQI change at week 24	-10.8 vs -7.6 (difference -3.2; nominal P=0.0026)

Dupilumab demonstrated clinically meaningful and statistically significant improvements in CSU symptoms regardless of baseline IgE levels . Both low IgE (<100 IU/mL) and high IgE (≥ 100 IU/mL) subgroups showed significant UAS7 reductions . However, comprehensive network meta-analysis suggests that the impact of dupilumab on quality of life remains uncertain, and no trials have addressed angioedema activity .

Safety data showed favorable tolerability, with treatment-emergent adverse events occurring in 50.0% with dupilumab versus 58.8% with placebo . Injection-site reactions were similar between groups (11.4% vs 13.2%), and serious adverse events were lower with dupilumab (2.9% vs 7.4%) .

Cyclosporine

Cyclosporine represents an established immunosuppressive option for refractory CSU.

Study	Dose	Outcome	Effect
C. Grattan et al., 2000	4mg/kg daily	UAS reduction at 4 weeks	12.7 (95% CI 6.6-18.8) vs 2.3 placebo (P=0.005)
C. Grattan et al., 2000	4mg/kg daily	Response rate	8/19 (42%) vs 0/10 placebo (P<0.05)
K. Kulthanan et al., 2017	Low-moderate doses	Response rate at 4 weeks	54%
K. Kulthanan et al., 2017	Low-moderate doses	Response rate at 12 weeks	73%
B. Kendziora et al., 2022	3-5mg/kg daily	UAS7 change	-10.40 (95% CI -19.40 to -1.40)

Cyclosporine at low to moderate doses (1-5mg/kg/day) achieves response rates of 54% at 4 weeks, 66% at 8 weeks, and 73% at 12 weeks . Network meta-analysis demonstrated comparable efficacy to omalizumab 300mg (UAS7 reduction -10.40 vs -10.45) .

However, cyclosporine has a less favorable safety profile. Adverse events are dose-dependent, occurring in 6% (very low dose), 23% (low dose), and 57% (moderate dose) of patients . The odds ratio for adverse events was 2.16 (95% CI 0.77-6.07) compared to placebo . Six of eight initial responders relapsed within 6 weeks of discontinuation , suggesting a suppressive rather than disease-modifying effect.

The comprehensive network meta-analysis concluded that cyclosporine may be among the most effective treatments but may be among the most harmful in increasing adverse event frequency .

Other Immunosuppressants

Treatment	Study	Comparison	UAS7 Effect (SMD)	Notes
Cyclosporine A + antihistamine	W. Bei et al., 2023	Network comparison	0.10 (95% CI 0.01-0.68)	Most effective
Azathioprine + antihistamine	W. Bei et al., 2023	Network comparison	0.03 (95% CI 0.00-0.23)	—
Tripterygium glycosides + antihistamine	W. Bei et al., 2023	Network comparison	0.52 (95% CI 0.32-0.85)	Effective alternative
Methotrexate + antihistamine	W. Bei et al., 2023	Network comparison	1.54 (95% CI 0.64-3.67)	—
Hydroxychloroquine	S. Nochaiwong et al., 2021a	vs Placebo	HRQOL SMD -1.00 (95% CI -1.61 to -0.39)	Higher risk of unacceptability

Network meta-analysis of four immunosuppressants found cyclosporine A combined with antihistamine resulted in greatest UAS7 improvements, while tripterygium glycosides also showed effectiveness. The evidence for azathioprine, dapsone, hydroxychloroquine, mycophenolate, sulfasalazine, and vitamin D remains uncertain.

Emerging and Novel Therapies

Barzolvolimab (Anti-KIT Antibody):

Barzolvolimab, a monoclonal anti-KIT antibody that depletes mast cells, showed rapid onset (1 week) and dose-dependent UAS7 reduction. At week 8, UAS7 reductions of -15.8, -19.6, and -22.7 were observed for the three lower dose cohorts versus -12.4 for

placebo . Common adverse events included urinary tract infections, headache, neutropenia, and back pain, with no adverse event-related discontinuations .

TLL-018 (TYK2/JAK1 Inhibitor):

In a phase 1b study, TLL-018 demonstrated high efficacy in moderate-to-severe CSU patients with inadequate response to antihistamines . At week 4, UAS7/ISS7 changes were -19.1/-10.3 with 10mg ($P<0.01$) and -23.6/-11.3 with 30mg ($P<0.0001$) versus -7.5/-2.3 with placebo . At week 12, 64.3% of patients on 10mg and 53.8% on 30mg achieved UAS7=0 .

H. pylori Eradication:

Antibiotics for H. pylori eradication increased CSU remission rates (RR 3.99; 95% CI 1.31-12.14) and improved symptoms (SMD 1.49; 95% CI 0.80-2.18) . H. pylori eradication was not associated with increased adverse events .

Adjunctive Therapies:

High-dose vitamin D3 supplementation (4,000 IU/day) as add-on therapy showed a 40% decrease in urticaria symptom severity scores by week 12, with beneficial trends for sleep quality and pruritus . No adverse events were reported .

Histaglobulin combined with bilastine achieved 89.9% UAS reduction versus 59.4% with bilastine alone by week 6 ($P<0.01$), with faster symptom resolution from week 2 .

Multi-strain probiotic as adjunctive therapy demonstrated superior control of itch severity compared to placebo, although no significant differences were observed for hives severity or urticaria control test outcomes .

Synthesis

Reconciling Treatment Efficacy Hierarchies

The evidence reveals a relatively consistent treatment hierarchy for antihistamine-refractory CSU. Network meta-analyses consistently identify omalizumab 300mg and high-dose ligelizumab as among the most effective interventions with large beneficial effects (SMD approximately -1.0). Remibrutinib and cyclosporine demonstrate comparable efficacy to omalizumab in UAS7 reduction (approximately -10 to -11 points vs placebo).

The apparent superiority of ligelizumab over omalizumab (SMD -1.05 to -1.07 vs -0.77) may reflect its higher IgE binding affinity. However, head-to-head comparative data remain limited, and the clinical significance of these differences requires confirmation in direct comparison trials.

Explaining Heterogeneity in Antihistamine Response

Approximately 50% of CSU patients have inadequate disease control at standard antihistamine doses, explaining the substantial unmet need driving research into alternative therapies. Predictors of non-response to H1-antihistamine-based treatments include treatment history, type of specialists seen, chronic pulmonary disease, depression, and female sex.

The heterogeneity in antihistamine efficacy data (with very wide confidence intervals in some meta-analyses, e.g., RR 52.88; 95% CI 3.31-843.81 for levocetirizine) reflects small study sizes and methodological limitations. The quality of evidence was affected by small numbers of studies in each comparison.

Dose-Response Relationships

A clear dose-response relationship exists for omalizumab, with 300mg achieving clinically meaningful benefits while 150mg does not. The 75mg dose showed no meaningful difference from placebo. For weekly itch score outcomes, 150mg dosage

showed the largest effect size (Cohen's $d = -2.6$), suggesting that outcome selection may influence apparent optimal dosing.

For antihistamines, increasing to twice the standard dose improves response rates (RR 1.12-1.13), but with diminishing returns and increased somnolence. The combination strategy of standard-dose antihistamine plus leukotriene antagonist achieves comparable efficacy to double-dose antihistamine with better tolerability.

Time to Response Considerations

Time to response varies considerably by treatment. Omalizumab shows some response as early as week 1 (3.9% achieving $UAS7 \leq 6$), with continued improvement through week 24. Patients with positive ASST respond more slowly (beyond 8 days), suggesting that autoimmune CSU may require longer treatment durations.

Remibrutinib demonstrates rapid onset from week 1, while cyclosporine response rates improve from 54% at 4 weeks to 73% at 12 weeks.

Safety-Efficacy Trade-offs

The safety-efficacy profile strongly favors omalizumab over cyclosporine. While both achieve similar efficacy (UAS7 reductions of approximately -10 points), cyclosporine's dose-dependent adverse events (up to 57% at moderate doses) and the comprehensive finding that cyclosporine "may be among the most harmful in increasing the frequency of any adverse events" position omalizumab as the preferred option for antihistamine-refractory CSU.

BTK inhibitors present an intermediate safety profile. Remibrutinib shows generally favorable safety similar to placebo, but with increased infection risk and petechiae. The safety profile of remibrutinib remains less certain than omalizumab.

Population-Specific Considerations

Evidence supports omalizumab efficacy across age groups (12-75 years) and baseline severity levels . Chinese patients showed similar responses to global populations . However, data on younger children, elderly patients, and ethnicity-specific responses remain limited .

For patients with IgE autoantibodies against thyroperoxidase, omalizumab demonstrated particular efficacy with 70.4% achieving complete wheal protection versus 4.5% with placebo , supporting biomarker-guided treatment selection.

Real-World vs. Trial Efficacy

Real-world evidence for omalizumab suggests benefits meeting or exceeding trial results, with complete response rates of 72.2% (95% CI 66.1%-78.3%) and adverse event rates of only 4.0% (95% CI 1.0%-7.0%) . This favorable real-world performance addresses concerns about generalizability of trial findings.

However, real-world studies identify substantial rates of non-response to antihistamine-based therapies (86.9% classified as non-responders in one cohort) , with non-responders experiencing increased hospitalizations and healthcare resource utilization .

Treatment Duration and Durability

The optimal treatment duration for omalizumab remains uncertain. RCT data extend to 24 weeks, with sustained benefits observed through this period . The average CSU duration of 1-2 years (longer with angioedema) suggests need for extended therapy in many patients. Six of eight cyclosporine responders relapsed within 6 weeks of discontinuation , indicating that immunosuppressive approaches are suppressive rather than curative.

The cumulative meta-analysis confirms that omalizumab efficacy has remained consistent over time, across different drug doses, and with improved precision from newer

studies . Current guidelines recommend omalizumab as an effective treatment, with 300mg for 12 weeks as a reasonable standard regimen .

DISCUSSION

This systematic review synthesizes evidence from 66 studies, offering a comprehensive overview of the contemporary management landscape for chronic spontaneous urticaria (CSU). The discussion integrates key findings, reconciles apparent discrepancies, explores clinical implications, and identifies future research directions.

1. Establishment and Refinement of First-Line Therapy:

The evidence robustly confirms second-generation H1-antihistamines (sgAHs) as the cornerstone of first-line CSU therapy. Network meta-analyses have helped delineate subtle differences within this class, with olopatadine, fexofenadine, bilastine, and levocetirizine showing consistently strong efficacy profiles (Phinyo et al., 2020). The review underscores the clinical dilemma faced when standard doses fail. The strategy of up-dosing sgAHs to two or even four times the licensed dose is supported by meta-analyses, demonstrating a statistically significant, albeit modest, improvement in response rates (RR 1.12-1.13) (Xiao et al., 2022, 2023). However, this benefit is counterbalanced by a clear increase in the risk of somnolence, a dose-limiting adverse effect (Zhou et al., 2022). This trade-off has prompted exploration of alternative strategies. Notably, combining a standard-dose sgAH with a leukotriene receptor antagonist (e.g., montelukast) was found to achieve symptom control comparable to double-dose antihistamine, but with significantly less sedation and better quality of life improvement, presenting a valuable alternative before escalating to advanced therapies (Sarkar et al., 2017).

2. Omalizumab: The Pivot Point in Refractory CSU Management:

For patients with inadequate control despite optimized antihistamine therapy, omalizumab represents a paradigm shift. The data are unequivocal: omalizumab 300 mg administered

subcutaneously every 4 weeks is highly effective. Pooled analyses show UAS7 reductions of approximately 10-11 points versus placebo, with complete response (UAS7=0) rates around 35-40% in trials and even higher (exceeding 70%) in real-world settings (Agache et al., 2020; Zhao et al., 2016; Tharp et al., 2019). Crucially, this efficacy is coupled with a safety profile indistinguishable from placebo in most meta-analyses, with injection-site reactions being the most common concern (Urgert et al., 2015). The review also highlights important nuances: a clear dose-response relationship exists, with the 150 mg dose showing inconsistent or minimal clinical benefit and the 75 mg dose being largely ineffective (Saini et al., 2011; Qin et al., 2024). Response can be rapid, with some improvement seen within a week, and benefits are sustained over at least 24 weeks of treatment (Casale et al., 2017). The consistency of omalizumab's efficacy across different populations, including Chinese patients, further solidifies its role as the global standard of care for antihistamine-refractory CSU (Yuan et al., 2022).

3. The Emergence of Novel and Next-Generation Agents:

The therapeutic horizon is expanding with agents targeting pathways beyond IgE. **Ligelizumab**, a next-generation anti-IgE monoclonal antibody with higher affinity, shows promise of potentially greater efficacy than omalizumab in network meta-analyses, though direct head-to-head confirmation is awaited (Nochaiwong et al., 2021; Khan et al., 2025). **Bruton's Tyrosine Kinase (BTK) Inhibitors**, such as remibrutinib, represent a novel oral mechanism targeting mast cell and basophil signaling. Phase 2 and 3 trials demonstrate rapid and profound UAS7 reductions, positioning them as a potent oral alternative (Maurer et al., 2022; Metz et al., 2025). However, their safety profile requires careful consideration; while generally favorable, meta-analyses indicate a significantly increased risk of infections (particularly upper respiratory) and a higher rate of adverse events compared to anti-cytokine biologics (Diamanti et al., 2025; Burhan et al., 2025). **Dupilumab**, blocking IL-4 and IL-13 signaling, has also demonstrated efficacy in CSU, independent of baseline IgE levels, offering a distinct mechanism for patients who may not respond to anti-IgE therapy (Maurer et al., 2022a, 2023a). Furthermore, highly innovative approaches

like **barzolvolimab** (an anti-KIT antibody that depletes mast cells) and **TLL-018** (a TYK2/JAK1 inhibitor) have shown remarkable efficacy in early-phase studies, heralding a new wave of targeted interventions (Maurer et al., 2023; Lu et al., 2024).

4. Re-evaluating the Role of Traditional Immunosuppressants:

Cyclosporine has long been a mainstay for severe, refractory CSU. The review confirms its efficacy, with UAS7 reductions comparable to omalizumab (Kendziora et al., 2022; Grattan et al., 2000). However, its utility is severely constrained by a problematic safety profile. Adverse events are frequent and dose-dependent, and network meta-analyses have flagged it as potentially among the most harmful treatments in terms of adverse event frequency (Kulthanan et al., 2017; Kendziora et al., 2022). Moreover, its effect is suppressive rather than disease-modifying, with high relapse rates upon discontinuation. In the current era, with the availability of safer and often more effective biologics and novel synthetics, the role of cyclosporine has diminished, typically reserved for specific cases or where access to newer agents is limited.

5. Reconciling Efficacy Hierarchies and Clinical Decision-Making:

Network meta-analyses attempt to create a hierarchy of treatments. While omalizumab and high-dose ligelizumab consistently rank at the top for large beneficial effects, and cyclosporine and remibrutinib show comparable efficacy in reducing UAS7, these statistical rankings must be interpreted with clinical pragmatism (Chu et al., 2025; Zhao et al., 2025). The choice between a highly effective but parenteral biologic with an excellent long-term safety record (omalizumab) and a highly effective oral agent with a slightly less certain safety profile (remibrutinib) will depend on patient preference, access, cost, and comorbidities. The safety-efficacy trade-off starkly favors omalizumab over cyclosporine, effectively repositioning the latter in the treatment algorithm.

6. Addressing Heterogeneity and Unmet Needs:

The review exposes significant heterogeneity in response to antihistamines and other therapies. Predictors of non-response to H1-antihistamines include female sex, depression, and specific comorbidities (Soong et al., 2023). Biomarkers like IgE anti-thyroperoxidase may predict excellent response to omalizumab (Maurer et al., 2011). A major unmet need remains the subset of patients who do not respond adequately to any current therapy. Furthermore, evidence gaps are evident for special populations (young children, elderly), long-term (>1 year) treatment outcomes, and the optimal strategy for de-escalating or discontinuing successful therapy. Adjunctive approaches, such as Vitamin D supplementation or *H. pylori* eradication in infected patients, show promise in specific contexts but require further validation (Rorie et al., 2014; Watanabe et al., 2021).

CONCLUSION

Conclusion

This comprehensive systematic review elucidates the current evidence-based management strategy for chronic spontaneous urticaria. Second-generation H1-antihistamines remain the foundational first-line treatment, with dose escalation or combination with leukotriene antagonists as logical next steps for partial responders. For the substantial proportion of patients with antihistamine-refractory disease, omalizumab 300 mg every 4 weeks stands as the established, highly effective, and safe standard of care in the third-line setting. The therapeutic landscape is rapidly evolving with the advent of novel agents such as ligelizumab, BTK inhibitors (remibrutinib), and dupilumab, which offer new mechanisms of action and potent efficacy, though their long-term safety and precise positioning relative to omalizumab require further definition. Traditional immunosuppressants like cyclosporine, while effective, are limited by their adverse effect profile and should be used judiciously. Promising emerging therapies targeting KIT or JAK pathways signal future advancements.

Recommendations:

1. **For Clinical Practice:** Adopt a stepwise approach per guidelines. For refractory CSU, prioritize omalizumab due to its robust efficacy and safety data. Consider novel agents like BTK inhibitors or dupilumab based on availability, patient preference (oral vs. injectable), and individual risk profiles, acknowledging the need for ongoing safety monitoring, particularly for infections with BTK inhibitors.
2. **For Researchers:** Future studies should prioritize head-to-head randomized controlled trials comparing newer agents (e.g., ligelizumab vs. omalizumab; remibrutinib vs. dupilumab). Long-term extension studies (>2 years) are crucial to establish durability of response and safety. Research must focus on identifying reliable clinical or serological biomarkers to predict treatment response and personalize therapy. Further investigation into the management of multi-refractory CSU and the efficacy of therapies in underrepresented populations is needed.
3. **For Policymakers:** Ensure guidelines are updated regularly to incorporate high-quality evidence on new therapies. Work towards improving patient access to effective but potentially costly biologic and novel therapies to reduce the disease burden and healthcare utilization associated with uncontrolled CSU.

REFERENCES

- A. Chu, Paul Oykhman, X. Chu, D. Rayner, Sukhdeep Bhargal, Andrew Dam, Janice Xu, et al. "Comparative Efficacy and Safety of Biologics and Systemic Immunomodulatory Treatments for Chronic Urticaria: Systematic Review and Network Meta-Analysis." *Journal of Allergy and Clinical Immunology*, 2025.
- A. Deshmukh, K. Godse, A. Deshmukh, Vatsal Patidar, and Vijayraghavan Seshadri. "A Prospective, Double-Blind, Placebo-Controlled Single-Center, Randomized Controlled Trial to Evaluate the Efficacy of a Multi-Strain Probiotic on Chronic Spontaneous Urticaria." *IP Indian Journal of Clinical and Experimental Dermatology*, 2025.

A. Fukunaga, Y. Oda, K. Washio, T. Omori, Y. Kakei, M. Hide, and C. Nishigori. “Efficacy of Switching to Bilastine, a Histamine H1 Receptor Antagonist, in Patients with Chronic Spontaneous Urticaria (H1-SWITCH): Study Protocol for a Randomized Controlled Trial.” *Trials*, 2020.

A. Giménez-Arnau, S. Ferrucci, M. Ben-Shoshan, Vincent Mikol, Laurence Lucats, Iris Sun, Leda Mannent, and J. Gereige. “Rilzabrutinib in Antihistamine-Refractory Chronic Spontaneous Urticaria.” *JAMA Dermatology*, 2025.

A. Kaplan, S. Spector, S. Meeves, Y. Liao, S. Varghese, and G. Georges. “Once-Daily Fexofenadine Treatment for Chronic Idiopathic Urticaria: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study.” *Annals of Allergy, Asthma & Immunology*, 2005.

A. Sil, S. Tripathi, A. Chaudhuri, N. Das, A. Hazra, Chiranjib Bagchi, and C. N. Islam. “Olopatadine Versus Levocetirizine in Chronic Urticaria: An Observer-Blind, Randomized, Controlled Trial of Effectiveness and Safety.” *Journal of Dermatological Treatment (Print)*, 2013.

Ana Carolina Putini Vieira, Ana Carolina Ventura de Santana de Jesus, Anelise Poluboiarinov Cappellaro, L. M. Barbosa, Ana Clara Felix de Farias Santos, Carolina Mira Dilly de Medeiros, Mable Pereira, Gabriel Gomes Lopes, and F. Zamora. “Efficacy and Safety of Ligelizumab in Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.” *Clinical Drug Investigation*, 2025.

Anastasia Diamanti, Chiara Tontini, and Silvia Bulfone-Paus. “Comparing Novel Treatments in Chronic Spontaneous Urticaria: A Critical Appraisal of Bruton's Tyrosine Kinase Inhibitors Versus Anti-cytokine Biologics in Clinical Trials.” *Clinical and Translational Allergy*, 2025.

Andy Rorie, W. Goldner, E. Lyden, and J. Poole. “Beneficial Role for Supplemental Vitamin D3 Treatment in Chronic Urticaria: A Randomized Study.” *Annals of Allergy, Asthma & Immunology*, 2014.

Atsushi Fukunaga, Y. Kakei, Sae Murakami, Yuji Kan, Koji Masuda, Masatoshi Jinnin, Ken Washio, et al. “Efficacy and Safety of Switching to Bilastine, an H1-Antihistamine, in Patients with Refractory Chronic Spontaneous Urticaria (H1-SWITCH): A Multicenter, Open-Label, Randomized, Parallel-Group Comparative Study.” *Frontiers in Immunology*, 2024.

B. Kendziora, J. Frey, M. Reinholz, F. Ruëff, E. Oppel, T. Zuberbier, D. Hartmann, J. G. Schlager, and L. French. “Efficacy and Safety of Medications for Antihistamine-Refractory Chronic Spontaneous Urticaria: A Systematic Review and Network Meta-Analysis.” *Allergo Journal International*, 2022.

C. Grattan, B. O'donnell, D. Francis, N. Niimi, R. Barlow, P. Seed, A. Kobza Black, and M. Greaves. “Randomized Double-blind Study of Cyclosporin in Chronic ‘Idiopathic’ Urticaria.” *British Journal of Dermatology*, 2000.

D. Carrillo, M. S. Borges, Elizabeth García, E. Egea, and C. Serrano. “Omalizumab Vs. Placebo in the Management of Chronic Idiopathic Urticaria: A Systematic Review.” *The World Allergy Organization Journal*, 2014.

E. Nettis, L. Cegolon, E. Di Leo, F. Lodi Rizzini, Aikaterini Detoraki, and G. Canonica. “Omalizumab Chronic Spontaneous Urticaria: Efficacy, Safety, Predictors of Treatment Outcome, and Time to Response.” *Annals of Allergy, Asthma & Immunology*, 2018.

G. Jemec. “Through the Looking-glass, and What the Dermatologist Found There.” *British Journal of Dermatology*, 2015.

H. Jia, and Yan-ling He. “Efficacy and Safety of Omalizumab for Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.” *American Journal of Therapeutics*, 2020.

H. Nelson, R. Reynolds, and J. Mason. “Fexofenadine HCl Is Safe and Effective for Treatment of Chronic Idiopathic Urticaria.” *Annals of Allergy, Asthma & Immunology*, 2000.

Haiyan Qin, Xianjun Xiao, Di Qin, Peiwen Xue, Huilin Liu, Ying Li, and Yunzhou Shi. “Different Doses and Courses of Omalizumab for Patients with Chronic Spontaneous Urticaria: A Systematic Review with Meta-Analysis and Trial Sequential Analysis.” *The World Allergy Organization Journal*, 2024.

Haiyan Qin, Xianjun Xiao, Di Qin, Wei Cao, Lu Wang, Meng Xi, Zihao Zou, et al. “Temporal, Drug Dose, and Sample Size Trends in the Efficacy of Omalizumab for Chronic Spontaneous Urticaria: A Cumulative Meta-Analysis.” *Journal of Clinical Pharmacy and Therapeutics*, 2024.

Humayun Manzoor, Foha Razi, Amina Rasheed, Z. Sarfraz, Azza Sarfraz, K. Robles-Velasco, M. Félix, and I. Chérrez-Ojeda. “Efficacy of Different Dosing Regimens of IgE Targeted Biologic Omalizumab for Chronic Spontaneous Urticaria in Adult and Pediatric Populations: A Meta-Analysis.” *Healthcare*, 2022.

I. Agache, Claudio Rocha, A. Pereira, Yang Song, P. Alonso-Coello, I. Solá, Jessica Beltran, et al. “Efficacy and Safety of Treatment with Omalizumab for Chronic Spontaneous Urticaria: A Systematic Review for the EAACI Biologicals Guidelines.” *Allergy. European Journal of Allergy and Clinical Immunology*, 2020.

I. Agache, Claudio Rocha, Yang Song, P. A. Coello, I. Solá, Jessica Beltran, M. Posso, et al. “Efficacy and Safety of Treatment with Omalizumab for Chronic Spontaneous Urticaria- a Systematic Review for the EAACI Biologicals Guidelines,” 2020.

J. Chinen. “Faculty Opinions Recommendation of Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria.” 2013.

J. Watanabe, Junya Shimamoto, and K. Kotani. “The Effects of Antibiotics for Helicobacter Pylori Eradication or Dapsone on Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis.” *Antibiotics*, 2021.

K. Kulthanan, Pichanee Chaweeikulrat, C. Komoltri, S. Hunnangkul, P. Tuchinda, L. Chularojanamontri, and M. Maurer. "Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review." *Journal of Allergy and Clinical Immunology: In Practice*, 2017.

Kalpana Mali Ramanna, Thota Sai Sumanth, Deepthi Konda, Madhavi Eerike, Soundarya Priyadarsini Kalaiselvan, Chandru Elangovan, V. Konda, and Siddharam S Janti. "Effect of Combining Histaglobulin with Antihistamines in Patients with Chronic Spontaneous Urticaria in a Tertiary Care Hospital Setting- a Randomized Trial." *Archives of Dermatological Research*, 2025.

M. C. Urgert, M. T. V. D. Elzen, A. Knulst, Zbys Fedorowicz, and E. Zuuren. "Omalizumab in Patients with Chronic Spontaneous Urticaria: A Systematic Review and GRADE Assessment." *British Journal of Dermatology*, 2015.

M. Hide, A. Yagami, M. Togawa, A. Saito, and M. Furue. "Efficacy and Safety of Bilastine in Japanese Patients with Chronic Spontaneous Urticaria: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase II/III Study." *Allergology International*, 2017.

M. Maurer, K. Rosen, H. Hsieh, S. Saini, C. Grattan, A. Giménez-Arnau, S. Agarwal, et al. "Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria." *New England Journal of Medicine*, 2013.

M. Maurer, M. Metz, John Anderson, Neetu Talreja, H. Windom, Diego Alvarado, E. Crowley, et al. "Safety and Clinical Activity of Multiple Doses of Barzolvolimab, an Anti-KIT Antibody, in Patients with Chronic Spontaneous Urticaria." *Journal of Allergy and Clinical Immunology*, 2023.

M. Maurer, S. Altrichter, T. Bieber, T. Biedermann, M. Bräutigam, S. Seyfried, R. Brehler, et al. "Efficacy and Safety of Omalizumab in Patients with Chronic Urticaria Who Exhibit IgE Against Thyroperoxidase." *Journal of Allergy and Clinical Immunology*, 2011.

M. Maurer, T. Casale, S. Saini, M. Ben-Shoshan, A. Radin, B. Akinlade, E. Laws, and L. Mannent. "DUPILUMAB EFFICACY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA

BY IGE LEVEL: LIBERTY-CSU CUPID STUDY A.” *Annals of Allergy, Asthma & Immunology*, 2022.

M. Maurer, T. Casale, Sarbjot (Romi) Saini, M. Ben-Shoshan, A. Radin, B. Akinlade, C. Fan, et al. “Dupilumab Improves Urticaria Activity And Quality Of Life In Patients With Chronic Spontaneous Urticaria (CSU).” *Journal of Allergy and Clinical Immunology*, 2023.

M. Maurer, W. Berger, A. Giménez-Arnau, K. Hayama, V. Jain, A. Reich, S. Haemmerle, et al. “Remibrutinib, a Novel BTK Inhibitor, Demonstrates Promising Efficacy and Safety in Chronic Spontaneous Urticaria.” *Journal of Allergy and Clinical Immunology*, 2022.

M. Metz, A. Giménez-Arnau, M. Hide, Mark G. Lebwohl, Giselle S. Mosnaim, Sarbjit S. Saini, Gordon Sussman, et al. “Remibrutinib in Chronic Spontaneous Urticaria.” *New England Journal of Medicine*, 2025.

M. Metz, P. Staubach, A. Bauer, R. Brehler, Janine Gericke, Michael Kangas, J. Ashton-Chess, et al. “Clinical Efficacy of Omalizumab in Chronic Spontaneous Urticaria Is Associated with a Reduction of FcεRI-Positive Cells in the Skin.” *Theranostics*, 2017.

M. S. Khan, Yousra Nadeem, Muhammad Mudassar Bilal, Aiman Baloch, Manayl Rasheed, Hamna Jehandad, Noor Ul Ain, et al. “From Wheal to Wellness: Efficacy and Safety of Ligelizumab in Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis.” *Archives of Dermatological Research*, 2025.

M. Tharp, J. Bernstein, A. Kavati, B. Ortiz, K. MacDonald, K. Denhaerynck, I. Abraham, and Christopher S Lee. “Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-Analysis of “Real-World” Evidence.” *JAMA Dermatology*, 2019.

Maulina Sharma, C. Bennett, B. Carter, and S. Cohen. "H1-Antihistamines for Chronic Spontaneous Urticaria: An Abridged Cochrane Systematic Review." *Journal of American Academy of Dermatology*, 2015.

Maulina Sharma, C. Bennett, S. Cohen, and B. Carter. "H1-Antihistamines for Chronic Spontaneous Urticaria." *Cochrane Database of Systematic Reviews*, 2014.

Muhammad Burhan, Saad Ashraf, Ahila Ali, Iqra Shahid, Jalib Ahmed, Muhammad Shahmeer Ullah Shah, Neha Bhagwan Das, and A. Nashwan. "Safety and Efficacy of Remibrutinib for Chronic Spontaneous Urticaria, a Systematic Review and Meta-Analysis." *International Archives of Allergy and Immunology*, 2025.

Nishitha Gopal Rao, Haixia Jing, A. Kabir, and Rohit Surthi. "Omalizumab for the Treatment of Chronic Spontaneous Urticaria: A Systematic Review." *International Journal of Research in Dermatology*, 2021.

N.P.M. Rubini, L. Ensina, Edina Mariko Koga da Silva, F. Sano, and Dirceu Solé. "Effectiveness and Safety of Omalizumab in the Treatment of Chronic Spontaneous Urticaria: Systematic Review and Meta-Analysis." *Allergologia Et Immunopathologia*, 2019.

P. Phinyo, Pattaraporn Koompawichit, S. Nochaiwong, N. Tovanabutra, S. Chiewchanvit, and M. Chuamanochan. "Comparative Efficacy and Acceptability of Licensed Dose Second-Generation Antihistamines in Chronic Spontaneous Urticaria: A Network Meta-Analysis." *Journal of Allergy and Clinical Immunology: In Practice*, 2020.

Pei-Mei Zhou, Shihua Zeng, Li Fu, Hao Chen, and Lin Li. "Efficacy and Safety of Intensive Nonsedating Antihistamines for Chronic Spontaneous Urticaria: A Meta-Analysis of Randomized Controlled Trials." *International Archives of Allergy and Immunology*, 2022.

Qianjin Lu, Bin Yang, Lunfei Liu, Linfeng Li, Weijun Liu, Xu Yao, Xiaoyong Man, et al. "Efficacy and Safety of TLL-018 in Moderate to Severe Chronic Spontaneous Urticaria Patients with

Inadequate Response to H1 Antihistamine: Results from a Phase Ib Study.” *Journal of Allergy and Clinical Immunology*, 2024.

R. Hein. “Chronic Urticaria: Impact of Allergic Inflammation.” *Allergy. European Journal of Allergy and Clinical Immunology*, 2002.

S. Nochaiwong, M. Chuamanochan, C. Ruengorn, R. Awiphan, N. Tovanabutra, and S. Chiewchanvit. “Evaluation of Pharmacologic Treatments for H1 Antihistamine-Refractory Chronic Spontaneous Urticaria: A Systematic Review and Network Meta-Analysis.” *JAMA Dermatology*, 2021.

S. Nochaiwong, M. Chuamanochan, C. Ruengorn, R. Awiphan, N. Tovanabutra, S. Chiewchanvit, B. Hutton, and K. Thavorn. “Impact of Pharmacological Treatments for Chronic Spontaneous Urticaria with an Inadequate Response to H1-Antihistamines on Health-Related Quality of Life: A Systematic Review and Network Meta-Analysis.” *Journal of Allergy and Clinical Immunology: In Practice*, 2021.

S. Saini, C. Bindslev-Jensen, M. Maurer, J. Grob, E. Bülbül Başkan, Mary S. Bradley, J. Canvin, 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.” *Journal of Investigative Dermatology*, 2014.

S. Saini, K. Rosen, H. Hsieh, D. Wong, E. Conner, A. Kaplan, S. Spector, and M. Maurer. “A Randomized, Placebo-Controlled, Dose-Ranging Study of Single-Dose Omalizumab in Patients with H1-Antihistamine-Refractory Chronic Idiopathic Urticaria.” *Journal of Allergy and Clinical Immunology*, 2011.

T. Casale, Patrick H. Win, J. Bernstein, K. Rosen, M. Holden, A. Iqbal, B. Trzaskoma, et al. “Omalizumab Response in Patients with Chronic Idiopathic Urticaria: Insights from the XTEND-CIU Study.” *Journal of American Academy of Dermatology*, 2017.

T. Sarkar, A. Sil, Santasmita Pal, Chinmoy Ghosh, and N. Das. “Effectiveness and Safety of Levocetirizine 10 Mg Versus a Combination of Levocetirizine 5 Mg and Montelukast 10 Mg in Chronic Urticaria Resistant to Levocetirizine 5 Mg: A Double-Blind, Randomized, Controlled Trial.” *Indian Journal of Dermatology, Venereology and Leprology*, 2017.

W. Bei, J. Qian, Qu Zilu, Chen Kai, Jiang Ruili, H. Feng, and Liuqing Chen. “Comparing Four Immunosuppressive Agents for Chronic Spontaneous Urticaria-A Network Meta-Analysis.” *International Immunopharmacology*, 2023.

W. Carr, K. Sitz, V. Jain, A. Giménez-Arnau, K. Lheritier, I. Nikolaev, S. Haemmerle, and M. Maurer. “REMIBRUTINIB IMPROVES CHRONIC SPONTANEOUS URTICARIA IN PATIENTS IRRESPECTIVE OF CU-INDEX: RESULTS FROM PHASE 2B STUDY.” *Annals of Allergy, Asthma & Immunology*, 2022.

W. Soong, Dhaval Patil, I. Pivneva, James E Signorovitch, M. Wells, M. Balp, and M. Kuruvilla. “Disease Burden and Predictors Associated with Non-Response to Antihistamine-Based Therapy in Chronic Spontaneous Urticaria.” *The World Allergy Organization Journal*, 2023.

Weiru Yuan, Shuifang Hu, Min Li, Li-jia Yang, Lingling Liu, M. Zheng, Zaipei Guo, et al. “Efficacy and Safety of Omalizumab in Chinese Patients with Anti-histamine Refractory Chronic Spontaneous Urticaria.” *Dermatologic Therapy*, 2022.

Wen-Kuang Lin, Shwu-Jiuan Lin, Woan-Ruoh Lee, Chia-Chieh Lin, Weei-Chin Lin, Hua-Ching Chang, Chi-Tsun Cheng, and J. C. Hsu. “Effectiveness and Safety of Immunosuppressants and Biological Therapy for Chronic Spontaneous Urticaria: A Network Meta-Analysis.” *Biomedicines*, 2022.

Xian-jun Xiao, Peiwen Xue, Yun-zhou Shi, Junpeng Yao, Wei Cao, Leixiao Zhang, Zihao Zou, et al. “The Efficacy and Safety of High-Dose Nonsedating Antihistamines in Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.” *BMC Pharmacology and Toxicology*, 2023.

Xian-jun Xiao, Yun-zhou Shi, Junpeng Yao, Wei Cao, Leixiao Zhang, Zihao Zou, Siyuan Zhou, et al. “The Efficacy and Safety of High-Dose Nonsedating Antihistamines in Chronic Spontaneous Urticaria: A Systematic Review of Randomized Clinical Trials,” 2022.

Yulong Wen, Yidan Tang, Miao Li, and Y. Lai. “Efficiency and Safety of Desloratadine in Combination with Compound Glycyrrhizin in the Treatment of Chronic Urticaria: A Meta-Analysis and Systematic Review of Randomised Controlled Trials.” *Pharmaceutical Biology*, 2021.

Yunting Liang, X. Su, Rongbiao Lu, F. Huang, Yue Zheng, W. Lai, and Chun Lu. “Efficacy and Safety of Omalizumab on the Treatment of Chronic Spontaneous Urticaria: A Meta-Analysis,” 2018.

Z. Zhai, Yin Wei, T. Lei, Xingping Chen, P. Hu, Lan Chen, P. Wei, Kaocong Tian, and B. Peng. “Olopatadine Hydrochloride for the Treatment of Chronic Idiopathic Urticaria: A Multicentre, Double-Blind, Randomized, Parallel-Group, Controlled Clinical Trial,” 2015.

Zhuhan He, Shuocheng Qiu, Zhi-Wei Huang, Guoqiang Zhang, Qingqing An, Feng Qu, and Na Wang. “Comparison Between Chronic Spontaneous Urticaria and Chronic Induced Urticaria on the Efficacy of Omalizumab Treatment: A Systematic Review and Meta-analysis.” *Dermatologic Therapy*, 2022.

Zuo-Tao Zhao, Chunmei Ji, Wen-jun Yu, Ling Meng, T. Hawro, Ji-Fu Wei, and M. Maurer. “Omalizumab for the Treatment of Chronic Spontaneous Urticaria: A Meta-Analysis of Randomized Clinical Trials.” *Journal of Allergy and Clinical Immunology*, 2016.

Zuotao Zhao, Yaqi Zheng, Xiaoting Song, C. Peng, Shuanglu Liao, Peixin Zhang, Yen Tan, Xiaojie Huang, and Litao Zhang. “Biological and Target Synthetic Treatments for Chronic Spontaneous Urticaria: A Systematic Review and Network Meta-analysis.” *Clinical and Translational Allergy*, 2025.