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Biosimilars in chronic spontaneous urticaria: current evidence, clinical implications and future perspectives

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Abstract

Chronic spontaneous urticaria (CSU) is a debilitating condition characterized by recurrent wheals and/or angioedema lasting more than six weeks without identifiable triggers. The global prevalence is increasing, and patients with resistance to antihistamine therapies experience a significantly reduced quality of life (QoL). Omalizumab, a monoclonal anti-IgE antibody, represents the cornerstone of second-line therapy in antihistamine-refractory CSU. With the expiration of the originator patent, biosimilar versions of omalizumab are being developed and introduced, potentially improving access and reducing healthcare costs. This narrative review critically summarizes the currently available evidence on Omlyclo® (omalizumab-igec; CT-P39, Celltrion), including analytical comparability studies, regulatory evidence and the pivotal phase III clinical trial in CSU, while discussing regulatory, clinical and pharmacoeconomic implications. Available evidence supports comparable efficacy, safety and immunogenicity to reference omalizumab, although long-term real-world data remain limited. This review discusses the emerging role of omalizumab biosimilars in CSU, highlighting current evidence, remaining knowledge gaps and future perspectives.

Keywords

chronic spontaneous urticaria, omalizumab, omalizumab-igec, CT-P39, anti-IgE, biologics, biosimilars, pharmacoeconomics

Introduction

Chronic spontaneous urticaria (CSU) is a mast cell-driven disease characterized by recurrent wheals and/or angioedema persisting for more than six weeks, without identifiable or specific triggers. A substantial proportion of patients worldwide experience inadequately controlled CSU, resulting in a considerable burden on quality of life (QoL), healthcare utilization, and socioeconomic costs [1].

In more than half of CSU patients, the pathophysiologic mechanisms are autoimmune. Furthermore, type 2 inflammation-driven comorbidities coexist in many CSU patients. First-line recommended treatment is based on 2nd generation H_1-antihistamines, up-dosing up to 4-fold in poorly controlled patients with standard dosage. According to recent guidelines, despite the widespread use in the immunoallergy field of novel small molecules and targeted anti-interleukin biologics, omalizumab still represents the recommended second-line treatment in antihistamine-refractory CSU [2].

The introduction of omalizumab has substantially improved disease control and long-term management of antihistamine-refractory CSU, allowing sustained remission in a proportion of patients following treatment discontinuation, although definitive disease-modifying effects have not yet been conclusively demonstrated [3, 4]. Omlyclo® (omalizumab-igec; CT-P39, Celltrion) received marketing authorization from the European Commission as a biosimilar and was subsequently approved by the U.S. Food and Drug Administration (FDA), where it also obtained the specific designation of interchangeability. Because the regulatory meaning of interchangeability differs substantially between the United States (US) and European Union (EU), these concepts should not be considered synonymous [5]. This review summarizes current evidence regarding Omlyclo in CSU, focusing on pharmacological properties, clinical efficacy, safety, immunogenicity, and real-world implications.

Methods

This review was conducted as a narrative review. A structured literature search was performed using PubMed/MEDLINE and Scopus to identify studies on CSU, omalizumab, omalizumab biosimilars, CT-P39 (omalizumab-igec), biosimilarity, interchangeability, switching, pharmacoeconomics, and immunogenicity. The literature search was conducted between April 15 and May 20, 2026, before manuscript submission on May 25, 2026. Representative search strings included combinations of the following terms using Boolean operators ("AND" and "OR"): ("chronic spontaneous urticaria" OR CSU) AND ("omalizumab" OR "CT-P39" OR "omalizumab-igec" OR Omlyclo) AND ("biosimilar" OR biosimilarity OR interchangeability OR switching OR immunogenicity OR pharmacoeconomics). Additional targeted searches were performed for regulatory documents using the keywords "EMA biosimilar omalizumab", "FDA Omlyclo", and "AIFA biosimilars". Google Scholar was additionally used to identify recently published articles and to screen the reference lists of relevant publications for additional eligible sources. Regulatory documents from the European Medicines Agency (EMA), the U.S. FDA, and the Italian Medicines Agency (AIFA) were also consulted. Priority was given to randomized clinical trials, international guidelines, regulatory documents, and peer-reviewed reviews published up to May 2026. As this is a narrative review, no formal systematic review methodology was applied. Only articles published in English were considered. Reference lists of eligible articles and relevant review papers were manually screened to identify additional pertinent publications.

From omalizumab to biosimilars: clinical evidence and perspectives

Patients with CSU, particularly those with poorly controlled disease, experience a substantial impairment in health-related QoL that is often disproportionate to the apparent, although recurrent, cutaneous manifestations. The chronic and unpredictable nature of wheals and angioedema results in persistent pruritus, sleep disturbance, emotional distress, reduced concentration, and impaired work productivity, making CSU one of the most burdensome chronic skin diseases [6]. Beyond physical symptoms, uncontrolled CSU is associated with anxiety, depression and impaired patient-reported outcomes, with QoL scores comparable to those observed in other severe chronic diseases [7]. Consequently, current therapeutic strategies aim not only to reduce symptoms but also to achieve complete disease control and,

whenever possible, sustained clinical remission, which are associated with substantial improvements in QoL and psychological well-being [3, 4].

The central pathogenic event in CSU is inappropriate activation and degranulation of dermal mast cells, releasing vasoactive and proinflammatory preformed mediators and cytokines/chemokines, e.g., histamine, tryptase, platelet activation factor (PAF), chymase, TNF-α, IL-4, IL-5, IL-6, IL-31, but also newly synthesized lipid mediators like leukotrienes (LTC4, LTD4) and prostaglandin D2 [8]. Wheals and/or angioedema are the consequence of these mediators, causing vasodilatation, increased vascular permeability and pruritus. Basophils also contribute, although paradoxically many CSU patients exhibit basopenia and impaired basophil responsiveness, suggesting redistribution to tissues and functional dysregulation [9]. Current evidence indicates that CSU comprises at least two major immunological endotypes. Type I autoimmune ("autoallergic") CSU is characterized by IgE autoantibodies directed against self-antigens, whereas type IIb autoimmune CSU is mediated by IgG or IgM autoantibodies against FcεRIα or IgE. These endotypes differ in immunological profile, disease severity and therapeutic response, with patients affected by type IIb autoimmune CSU generally showing lower serum IgE levels and a less favourable response to omalizumab [10–12]. Activation of the coagulation and complement cascades may amplify mast-cell activation and vascular permeability, contributing to disease severity [13]. Neuroimmune interactions, particularly substance P-mediated activation of the Mas-related G protein-coupled receptor X2 (MRGPRX2), may further amplify mast-cell activation and contribute to symptom exacerbation independently of IgE [14]. Additional emerging mechanisms include gut microbiota alterations and chronic low-grade inflammation, although their clinical relevance remains under investigation [15].

The management of CSU follows a stepwise, evidence-based therapeutic algorithm aimed at achieving complete symptom control while minimizing treatment-related adverse effects. International guidelines recommend a progressive escalation strategy based on disease activity and response to therapy, reflecting the heterogeneous pathophysiology of CSU and its variable treatment responsiveness. First-line treatment consists of second-generation H_1-antihistamines administered at standard doses, which target histamine-mediated symptoms by blocking H_1 receptors on endothelial cells and sensory nerves. These agents are preferred due to their favorable safety profile and minimal sedative effects. However, a substantial proportion of patients remain symptomatic under standard dosing. In such cases, guidelines recommend up-dosing antihistamines up to fourfold, a strategy supported by evidence demonstrating improved efficacy without significant increases in adverse events (AEs). For patients who remain uncontrolled despite high-dose antihistamines, the addition of targeted biologic therapy with omalizumab represents the recommended approach [2].

The recommended dosing of omalizumab is 300 mg administered subcutaneously every 4 weeks, as established by pivotal clinical trials and endorsed by international guidelines such as those from the EAACI/GA^{2}LEN/EDF/WAO [2]. However, these guidelines also acknowledge the need for individualized treatment strategies in patients with inadequate response. In particular, dose escalation up to 450–600 mg every 4 weeks or interval shortening to every 2 weeks may be considered in partial or non-responders, based on real-world evidence and expert consensus, although such approaches remain off-label in many settings [16]. Conversely, in patients achieving sustained disease control, dose reduction or interval prolongation (e.g., extending administration to every 6–8 weeks) can be attempted to minimize treatment burden and costs. These flexible dosing strategies reflect the heterogeneous nature of CSU and aim to optimize the balance between efficacy, safety and resource utilization, emphasizing the importance of a personalized, treat-to-target approach guided by disease activity scores and patient-reported outcomes [2, 3].

Although omalizumab provides rapid and sustained disease control in a large proportion of patients, treatment response remains heterogeneous. Approximately 50–70% of antihistamine-refractory patients achieve a significant clinical response with the licensed 300 mg dose, whereas complete or near-complete disease control is observed in approximately 35–45% of patients. Among partial responders, dose escalation may improve outcomes; however, approximately 10–20% of patients remain inadequately

controlled despite optimized anti-IgE therapy, highlighting the need for additional therapeutic options and reliable predictive biomarkers [2, 16–18].

In patients who do not achieve significant disease control with omalizumab, successive and suggested therapeutic options include anti-IL-4 receptor alpha dupilumab, Bruton's tyrosine kinase inhibitor remibrutinib (where approved or available) or immunosuppressive therapies such as cyclosporine A, which act by inhibiting T-cell activation and indirectly reducing mast cell activity. Short courses of systemic corticosteroids may be used for acute exacerbations, but are not recommended for long-term management due to their unfavorable safety profile [2, 19]. Overall, the current treatment algorithm reflects the progressive transition from empirical symptom control toward precision medicine, in which treatment decisions are increasingly guided by disease endotypes, clinical characteristics and predictors of therapeutic response. Within this framework, omalizumab represents the established first-line biologic therapy for antihistamine-refractory CSU and therefore serves as the reference product against which biosimilar development has been evaluated.

Biologics are therapeutic molecules characterized by structurally complex active substances obtained through biotechnological processes involving living systems, including recombinant DNA technology, cell culture, or microbial fermentation. Due to their inherent variability and sensitivity to production conditions, biologics require rigorous control of manufacturing processes to ensure consistent clinical performance [20].

Omalizumab (Xolair®, Genentech) was the first successful biologic drug used in allergic disease. It is a recombinant humanized monoclonal antibody IgG1 that selectively binds to the C3 domain of the circulating IgE, thereby preventing its interaction with both the high-affinity (FcεRI) and low-affinity (FcεRII/CD23) IgE receptors expressed on mast cells, basophils and other immune cells. This interaction results in reduced free IgE levels, progressive downregulation of FcεRI expression and subsequent inhibition of mast-cell and basophil activation, ultimately decreasing the release of histamine and other pro-inflammatory mediators [21]. The efficacy of omalizumab in CSU extends beyond simple IgE neutralization. Progressive downregulation of FcεRI expression, restoration of basophil responsiveness and modulation of autoimmune inflammatory pathways contribute to the rapid clinical improvement observed in many patients, including those without classical IgE-mediated allergy.

Recent advances in the understanding of CSU endotypes have further refined the positioning of omalizumab. Patients with higher baseline IgE levels, absence of functional autoantibodies, and a Th2-dominant profile tend to exhibit better responses, whereas those with type IIb autoimmune CSU may respond less favorably and require alternative or adjunctive approaches [12]. Nonetheless, omalizumab remains a cornerstone of therapy due to its broad efficacy across patient subgroups and its ability to significantly improve QoL. Because omalizumab has become the standard biologic therapy for antihistamine-refractory CSU, it also represents the reference product against which all subsequent biosimilar candidates have been analytically and clinically compared.

Omalizumab has been available in clinical practice for more than two decades. It was first approved by the U.S. FDA in 2003 for severe allergic asthma, followed by EMA approval in 2005 and subsequent reimbursement in Italy by the AIFA in 2006. Over time, its therapeutic indications have progressively expanded to include CSU, chronic rhinosinusitis with nasal polyps (CRSwNP) and, in the US, IgE-mediated food allergy (Table 1). The broad clinical experience accumulated across multiple immune-mediated diseases has generated a robust body of evidence supporting the long-term efficacy and safety of reference omalizumab, providing the scientific foundation upon which biosimilar development has been based.

Despite its efficacy, access to omalizumab has historically been limited by its high acquisition cost. The expiration of market exclusivity has therefore created the opportunity to introduce biosimilars, with the potential to expand patient access while improving the sustainability of healthcare system burden [22, 23].

A biosimilar is a biologic medicinal product that has been demonstrated, through a comprehensive comparability exercise, to be highly similar to an already authorized reference biological product, in terms of structure, biological activity, pharmacokinetics (PKs), efficacy, safety and immunogenicity, without

Table 1. Omalizumab: regulatory timeline and approved indications [2, 25, 28].

Region	Year	Indication	Notes
United States	2003	Moderate-to-severe allergic asthma	First FDA approval (≥ 12 years; later extended to younger patients)
Europe	2005	Moderate-to-severe allergic asthma	Initial EMA approval
Italy	2006	Moderate-to-severe allergic asthma	AIFA reimbursement and clinical use
Europe	2014	Chronic spontaneous urticaria (CSU)	For patients uncontrolled with H_1-antihistamines
Italy	2015	Chronic spontaneous urticaria (CSU)	AIFA reimbursement
Europe	2020	Chronic rhinosinusitis with nasal polyps (CRSwNP)	Add-on therapy in severe disease
United States	2020	Chronic rhinosinusitis with nasal polyps (CRSwNP)	Similar indication to EMA
United States	2024	IgE-mediated food allergy	Reduction of risk of severe allergic reactions

clinically meaningful differences [24]. Unlike generic drugs, biosimilars cannot be considered identical copies because of the intrinsic complexity of biologic manufacturing. Consequently, regulatory approval relies on a stepwise demonstration of biosimilarity beginning with extensive analytical characterization, followed by non-clinical studies when required and confirmatory clinical investigations designed to exclude clinically meaningful differences from the reference product rather than to re-establish clinical efficacy de novo. The European regulatory framework for biosimilars is well established and relies on a centralized authorization process coordinated by the EMA. However, approval of biosimilarity should be distinguished from policies governing interchangeability and substitution, which remain the responsibility of individual national regulatory authorities [25, 26]. In Italy, AIFA considers EMA-approved biosimilars therapeutically equivalent to their reference products and supports switching decisions based on clinical judgement, while maintaining that automatic substitution remains outside the pharmacist's authority (Table 2).

Table 2. Regulatory and policy landscape of biosimilars in the European Union (EU), Italy, and the United States (US).

Aspect	EU	Italy	US
Marketing authorisation	EMA centralised (mandatory)	EMA approval valid nationally	FDA approval
Biosimilarity	Based on totality of the evidence	Same as EMA	Same as FDA
Interchangeability	Scientific principle recognized; implementation determined nationally	Physician-directed switching; no automatic substitution	Separate FDA interchangeability designation
Switching	Physician decision	Physician decision	Physician decision
Pharmacy-level substitution	Not harmonized across EU	Not permitted	Permitted only for FDA-designated interchangeable biosimilars, according to state law
Pricing/Access	Not centralised	Regional/National control	Market-based
Reimbursement	National health systems	No active AIFA monitoring registry currently required for CSU	Individual payer systems

Data are from EMA biosimilar guidance, AIFA position papers and FDA biosimilar guidance [22, 25, 28].

Beyond currently approved anti-IgE therapies, several next-generation biologics and biosimilar-oriented molecules are expanding the therapeutic landscape. In the recent WAO state-of-the-art review by Canonica et al. [27], emerging anti-IgE strategies were highlighted as part of the evolving precision medicine approach in allergic diseases. Novel agents include high-affinity anti-IgE monoclonal antibodies, long-acting molecules, and IgE-trap fusion proteins designed to achieve deeper IgE suppression and prolonged disease control. Among these compounds, LP-003 (LongBio Pharma) is a next-generation long-acting anti-IgE monoclonal antibody characterized by markedly increased IgE-binding affinity and enhanced inhibition of FcεRI and CD23 signaling compared with omalizumab. Another innovative anti-IgE biologic is UB-221 (United BioPharma), a humanized monoclonal antibody with a mechanism distinct from

that of omalizumab. UB-221 appears capable of inducing CD23-mediated downregulation of circulating IgE while reducing mast-cell and basophil activation. In parallel, IgE-trap technologies are also under development. GI-301, developed by GI Innovation, is a recombinant IgE Trap-Fc fusion protein designed to neutralize free IgE and interfere with FcεRIα-mediated mast-cell activation. This platform may provide broader IgE neutralization capacity, including in patients with very high IgE levels, while potentially reducing immunogenicity and anaphylaxis risk. Furthermore, biosimilar and biosuperior anti-IgE programs, including Ozureprubart, currently under investigation, may contribute to improving accessibility and expanding therapeutic options in severe allergic diseases over the next decade. Although most of these agents remain in early clinical development, they collectively represent an important step toward more potent, durable, and individualized IgE-targeted therapy.

At present, the patent protection for omalizumab (Xolair®, Genentech) expired in Europe in September 2025, enabling the entry of biosimilars into the market. The first omalizumab biosimilar Omlyclo (omalizumab-igec; CT-P39, Celltrion), was approved by the European Commission in May 2024 and by the U.S. FDA in March 2025. Unlike the European regulatory framework, the FDA also granted CT-P39 an interchangeability designation, allowing pharmacy-level substitution according to applicable U.S. state legislation. While regulatory approval in Europe preceded patent expiry, the actual market introduction in European countries, including Italy, occurred between late 2025 and early 2026, following national pricing and reimbursement procedures [28].

Omlyclo shares the same amino acid sequence and mechanism of action as the reference product and has been approved for all indications of reference omalizumab, including CSU, allergic asthma, CRSwNP, while approval for IgE-mediated food allergy currently applies only in the US. Approval was supported by a stepwise biosimilarity development programme, beginning with extensive analytical characterization and followed by comparative PK and pharmacodynamic (PD) studies demonstrating equivalent systemic exposure (AUC and Cmax within predefined bioequivalence margins) in healthy volunteers. These data formed the basis for the subsequent confirmatory phase III trial (NCT04426890) in CSU [29, 30]. This pivotal randomized double-blind active-controlled trial included 619 patients with CSU inadequately controlled by H_1-antihistamines. Patients were randomized to receive CT-P39 or reference omalizumab at either 150 mg or 300 mg every four weeks for 24 weeks, followed by a 16-week observational follow-up. An important feature of the study was the predefined rerandomization at week 12, during which 96 patients switched from reference omalizumab to CT-P39, allowing preliminary evaluation of a single-switch strategy [31]. The primary endpoint of the study focused on change in weekly itch severity score (ISS7) at week 12, analyzed within predefined equivalence margins. Secondary endpoints included Urticaria Activity Score over 7 days (UAS7), Dermatology Life Quality Index (DLQI), safety, PKs and immunogenicity. CT-P39 met the predefined criteria for therapeutic equivalence, with improvements in ISS7, UAS7 and DLQI comparable to those achieved with reference omalizumab throughout the treatment period.

Safety outcomes were also comparable between treatment groups. The incidence of treatment-emergent AEs, serious AEs, injection-site reactions and hypersensitivity reactions was similar for CT-P39 and reference omalizumab. Immunogenicity remained low, with comparable rates of anti-drug antibody (ADA) development and no clinically meaningful impact on efficacy or safety. Nevertheless, the duration of follow-up was relatively limited, and the sample size was insufficient to detect uncommon AEs or delayed immune responses, highlighting the importance of continued post-marketing pharmacovigilance [30, 31] (Table 3).

Although the phase III trial successfully demonstrated biosimilarity according to regulatory requirements, it should not be interpreted as a superiority or efficacy trial. Rather, its objective was to exclude clinically meaningful differences between CT-P39 and the reference product within predefined equivalence margins. Consequently, the overall evidence supporting CT-P39 results from the integration of analytical, functional, PK, immunogenicity and clinical comparability data rather than from the phase III study alone. Despite these encouraging findings, several uncertainties remain regarding the routine implementation of omalizumab biosimilars in clinical practice. These study results may not fully reflect several characteristics and complexities encountered in real-life clinical practice: switching data, when

Table 3. Pivotal clinical evidence supporting omalizumab-igec (CT-P39) in chronic spontaneous urticaria [30, 31].

Characteristic	Evidence
Study	Phase III, randomized, double-blind, active-controlled equivalence trial [31]
Clinical Trials	NCT04426890
Population	619 adults with H_1-antihistamine-refractory CSU
Treatment	CT-P39 (omalizumab-igec) 300 mg every 4 weeks
Comparator	Reference omalizumab 300 mg every 4 weeks
Treatment duration	24 weeks
Follow-up	16-week
Primary endpoint	Change in ISS7 (weekly itch severity score) at week 12
Primary outcome	Primary equivalence endpoint met within the predefined equivalence margin; comparable reduction in ISS7 vs. reference omalizumab (−9.21 vs. −9.98)
Secondary outcomes	Comparable improvements in UAS7, DLQI, angioedema activity and other efficacy outcomes between CT-P39 and reference omalizumab
Safety	Similar overall incidence of adverse events and serious adverse events
Immunogenicity	Comparable anti-drug antibody incidence with no clinically meaningful differences
Switching substudy	Single-switch from reference omalizumab to CT-P39 maintained comparable efficacy, safety and immunogenicity
Main limitations	One pivotal Phase III equivalence study; absence of multiple-switching data and limited long-term real-world evidence

included, are generally limited to single-transition designs from originator to biosimilar with short observation periods, leaving uncertainty regarding multiple switching strategies and long-term interchangeability in real-world CSU management. Furthermore, potential resistance from both physicians and patients to switching from the originator to the biosimilars remains a relevant barrier in clinical practice. Physicians may express concerns regarding extrapolation of indications, immunogenicity and the robustness of real-world evidence supporting long-term efficacy and safety, particularly in a condition characterized by fluctuating disease activity and high unmet needs. From the patient perspective, reluctance is often driven by the nocebo effect, fear of loss of disease control after achieving stability with the originator, and limited understanding of biosimilar regulatory standards. Additionally, organizational factors, including a lack of clear switching protocols and inconsistent communication strategies, may further contribute to hesitancy. Addressing these challenges requires targeted educational interventions, transparent discussion of available evidence, and shared decision-making to enhance confidence in biosimilar use and facilitate their integration into routine management of CSU.

Overall, the currently available evidence supports the biosimilarity of CT-P39 with respect to efficacy, safety and immunogenicity. However, the available evidence remains centred on one pivotal equivalence trial together with analytical and PK comparability studies. Consequently, continued post-marketing pharmacovigilance, long-term observational cohorts and real-world effectiveness studies will be essential to confirm sustained clinical performance across broader patient populations.

Future research should also be supported by disease-specific real-world registries. The experience of the Severe Asthma Network Italy (SANI) has demonstrated the value of large observational cohorts in understanding long-term biologic effectiveness, safety, and treatment persistence. Similar registries dedicated to CSU may substantially improve knowledge regarding biosimilar performance in routine clinical practice and facilitate the generation of larger pharmacovigilance datasets. Such datasets may, in turn, contribute to biomarker discovery through big-data analytics and machine-learning approaches, further advancing precision medicine strategies in CSU. The therapeutic landscape of CSU is expected to evolve further with increasing refinement in the use of anti-IgE therapy and the progressive introduction of biosimilars. While omalizumab remains the most effective second-line treatment for antihistamine-refractory CSU, a key unmet need is the identification of reliable predictive biomarkers to optimize patient selection, anticipate therapeutic response, and guide treatment duration [3]. Although several candidate biomarkers have been proposed, these include total serum IgE levels, basophil activation test (BAT)

reactivity, expression of FcεRI on basophils, and clinical characteristics such as disease duration, presence of type IIb autoimmune CSU, and rapidity of response within the first 4–12 weeks of therapy. However, none of these markers has yet achieved sufficient sensitivity and specificity for routine clinical use. Integrative approaches combining immunological, genetic, transcriptomic, and machine-learning-based signatures may offer improved predictive accuracy in the future [32]. Although real-world data specific to Omlyclo remain limited, extensive clinical experience with reference omalizumab provides important contextual evidence regarding long-term effectiveness, safety, and treatment persistence. Nevertheless, biosimilar-specific outcomes should not be inferred automatically from originator data, emphasizing the importance of continued post-marketing surveillance and dedicated observational studies.

Cost savings

The introduction of biosimilars, such as Omlyclo, has several implications in terms of cost reduction and increased accessibility to biologics, broader patient eligibility, potential earlier use of biologics in the future, and reduced disease burden [33].

Switching from the originator to an omalizumab biosimilar in CSU may generate cost savings, primarily because biosimilars are generally introduced at lower acquisition costs than the reference product, although the magnitude of these savings varies across healthcare systems. Real-world pharmacy price listings in Europe typically estimate a lower price in the range of 20–50% compared with the reference product based on experience with other monoclonal antibodies. Although direct real-world economic data specific to omalizumab biosimilars in CSU are still emerging, extrapolation from cost-effectiveness and budget impact models indicates that drug costs represent the dominant component of total expenditure, with omalizumab therapy costing approximately €745 per 4 weeks in European settings [23]. Consequently, even modest price reductions can translate into meaningful savings at the population level. The first available pricing data for the omalizumab biosimilar Omlyclo confirm a consistent reduction in drug acquisition costs compared with the originator Xolair. Pharmacy prices in Italy suggest that a 150 mg prefilled syringe of Omlyclo is approximately 50% less expensive than the reference product, data aligned with broader estimates indicating that biosimilars are typically introduced at lower prices than originators. When translated into annual treatment costs for CSU, these differences may correspond to estimated annual savings approaching €5,000 per patient/year under the current Italian pricing scenario; however, these estimates remain dependent on local pricing, reimbursement policies and procurement procedures (Table 4).

Table 4. Estimated cost savings with biosimilar omalizumab in CSU [23, 24, 34].

Parameter	Reference omalizumab	Biosimilar (–20%)	Biosimilar (–30%)	Biosimilar (–50%)
Cost for 4 weeks (€) *	745	596	522	372
Estimated annual cost per patient (€)	9,685	7,750	6,780	4,840
Estimated annual savings per patient (€)	-	1,935	2,905	4,840
Relative saving	-	20%	30%	50%

* Assuming standard CSU dosing of 300 mg every 4 weeks (13 administrations/year). Values represent illustrative scenarios derived from published European pharmacoeconomic analyses and currently available pricing information. Actual prices and healthcare savings may vary depending on national procurement systems, reimbursement policies, market competition, and local tender procedures.

A budget impact analysis by Jang et al. [34] suggested that the introduction of omalizumab biosimilars could generate substantial healthcare savings over a multi-year horizon under specific pricing and market uptake assumptions. In their model, these projected savings were primarily driven by lower acquisition costs and increasing biosimilar adoption, with the potential to improve patient access without increasing the overall healthcare system costs. According to a 23-country European budget impact model, a 30% price discount yielded €40 million in first-year savings and €640 million over 5 years, allowing nearly 96,000 additional patients to be treated. Savings increased to €1.04–1.44 billion under higher discount scenarios. These estimates should be interpreted cautiously because actual savings depend on multiple factors

including national pricing policies, tender procedures, reimbursement systems, market penetration and potential reductions in originator pricing following biosimilar competition. Additionally, long-term analyses suggest that while omalizumab increases direct drug costs compared with the standard of care, improvements in disease control may partially offset costs through reductions in indirect burden [33]. Overall, currently available pharmacoeconomic models suggest that omalizumab biosimilars may improve healthcare sustainability and patient access. However, these findings remain model-based and require confirmation through country-specific real-world economic evaluations.

Limitations

The evidence supporting omalizumab biosimilars in CSU has several limitations. First, clinical evidence is largely derived from a single pivotal equivalence trial with a relatively limited follow-up period. Second, long-term real-world effectiveness, persistence, pharmacovigilance, and multiple-switching data remain scarce. Third, available pharmacoeconomic evaluations are primarily based on modelling studies and therefore may not accurately reflect country-specific pricing and reimbursement policies. These limitations should be considered when interpreting the current evidence base and highlight the need for continued post-marketing surveillance.

Conclusion

The management of CSU has evolved substantially with the introduction of targeted biologic therapies such as omalizumab, which have demonstrated significant efficacy and safety in patients refractory to antihistamines. Current international guidelines support a flexible, patient-centered approach, allowing for dose escalation or interval adjustment in non-responders, as well as de-escalation strategies in patients achieving sustained disease control. In parallel, the approval of the first omalizumab biosimilar Omlyclo (omalizumab-igec) represents an important milestone in the management of CSU. Supported by the totality of evidence required for biosimilar approval—including analytical, PK, immunogenicity and clinical comparability studies, as well as a pivotal clinical trial—Omlyclo represents a promising therapeutic option that has demonstrated comparable efficacy, safety and immunogenicity to the reference product. Nevertheless, barriers to switching, including physician concerns and patient-related nocebo effects, must be carefully addressed through education and shared decision-making. Although the currently available data are reassuring, continued pharmacovigilance, long-term real-world studies and dedicated observational registries remain essential to further characterize long-term effectiveness and safety in routine clinical practice. Future advances in precision medicine, including the identification of reliable predictive biomarkers, may further optimize patient selection and contribute to a more individualized use of both originator and biosimilar anti-IgE therapies. Although Omlyclo is currently the only approved omalizumab biosimilar for CSU, its introduction marks the beginning of a broader evolution in biologic therapy, highlighting the need for continued evidence generation. As additional real-world evidence becomes available, long-term effectiveness, pharmacovigilance outcomes, multiple-switching strategies, treatment persistence and the real economic impact of biosimilar implementation should be further evaluated in routine clinical practice. The successful integration of biosimilars into routine clinical practice will ultimately depend not only on robust scientific evidence but also on clinician confidence, patient engagement, transparent communication to minimize nocebo effects, and the continued generation of high-quality real-world evidence. Ultimately, irrespective of the therapeutic strategy adopted, achieving complete and sustained disease control remains the primary therapeutic goal in CSU and the cornerstone of long-term patient management.

Abbreviations

AEs: adverse events

AIFA: Italian Medicines Agency

CRSwNP: chronic rhinosinusitis with nasal polyps

CSU: chronic spontaneous urticaria

DLQI: Dermatology Life Quality Index

EMA: European Medicines Agency

FDA: Food and Drug Administration

ISS7: weekly itch severity score

PKs: pharmacokinetics

QoL: quality of life

UAS7: Urticaria Activity Score over 7 days

US: United States

Declarations

Author contributions

AS: Conceptualization, Writing—original draft. EN and CD: Conceptualization, Investigation, Supervision. MC and GWC: Validation, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Eustachio Nettis, who is an Editorial Board Member, and Giorgio Walter Canonica, who is Editor-in-Chief of *Exploration of Asthma & Allergy*, were not involved in the peer review or editorial decision-making process for this manuscript. Giorgio Walter Canonica reports having received research grants and/or lecturer or advisory board fees from A. Menarini, AstraZeneca, Celltrion, Chiesi Farmaceutici, Faes, Firma, Genentech, GrandPharma, Guidotti, GlaxoSmithKline, HAL Allergy, Novartis, OM Pharma, Organon, RedMaple, Sanofi-Genzyme, Stallergenes Greer, and Uriach Pharma. The remaining authors declare that they have no conflicts of interest.

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