v. 5, n. 4, 2025

International Journal of Health Science

Acceptance date: 14/01/2025

BIOLOGICS IN THE TREATMENT OF CHRONIC SPONTANEOUS URTICARIA: MECHANISMS, EFFICACY AND FUTURE PROSPECTS

Julia Sambi Freitas
Pontifícia Universidade Católica de Campinas (PUCCAMP)
Campinas - São Paulo
https://orcid.org/0009-0008-8448-3332

Bruna Belani dos Santos Oliveira
Centro Universitário Lusíada (UNILUS)
Santos - São Paulo
https://orcid.org/0009-0000-4343-1407

Gabriella Almeida Santos de Santana
Universidade Federal da Bahia
Vitória da Conquista - Bahia
https://orcid.org/0000-0001-9391-3076

Vitoria Azevedo Costa
Universidade Federal Fluminense
Niterói - Rio de Janeiro
https://orcid.org/0009-0005-9418-2435

Clara Liz Ançay Coelho
Centro Universitário de Jaguariúna (UNIFAJ)
Jaguariúna - São Paulo
https://orcid.org/0009-0005-4449-0800

Mariana Carvalho Murari
Universidade Anhembi Morumbi (UAM)
Piracicaba - São Paulo
https://orcid.org/0009-0009-2366-1198

Lorene Alarcão Viza
Centro Universitário IMEPAC (IMEPAC)
Araguari - Minas Gerais
https://orcid.org/0009-0008-2099-1899

Larissa Lima Kurata
Universidade Santo Amaro (UNISA)
São Paulo - São Paulo
https://orcid.org/0009-0000-5903-4246

Thaís Araújo dos Santos
Universidade Federal do Rio Grande do Norte (UFRN)
Caicó - Rio Grande do Norte
https://orcid.org/0000-0002-7833-0363

Giselle Guarezi Martins
Universidade do Extremo Sul Catarinense (UNESC)
Criciúma - Santa Catarina
https://orcid.org/0009-0004-5383-9472

Mariana Trindade de Oliveira
Universidade para o Desenvolvimento do Estado e da Região do Pantanal (UNIDERP)
Campo Grande - Mato Grosso do Sul
https://orcid.org/0009-0008-9594-6523

Priscila Santana de Jesus
Universidad Nacional de Rosario (UNR)
https://orcid.org/009-0002-5018-1455

Abstract: Objective: To analyze the role of biologics, particularly omalizumab and other off-label biologic therapies, in the management of chronic spontaneous urticaria, discussing mechanisms of action, efficacy, biomarkers of response and future prospects for new treatments. **Methodology:** Narrative literature review using the PubMed database. The search terms included "urticaria", "treatment", "monoclonal antibody", "omalizumab", "biologic treatment" and their combinations. After applying the inclusion and exclusion criteria, a total of 18 articles, published between 2019 and 2024, were selected for detailed analysis. **Discussion:** The use of immunobiologicals in the treatment of UCE is effective and safe, and is considered the first line of treatment in refractory cases. However, it has some limitations, especially in relation to the patient's clinical profile, requiring treatment to always be individualized. In addition, there is a need for further studies to clarify gaps in the literature, such as factors related to the use of immunobiologicals and their mechanisms of action in special cases, such as immunosuppressed patients. **Final considerations:** A significant improvement in physical and psychological symptoms was observed with the use of Omalizumab in patients with UCE. However, studies are still needed that explore all age groups, consider adjustments to the prescribed dose and include specific clinical characteristics, such as obesity and limited levels of total IgE.

Keywords: Chronic spontaneous urticaria, Omalizumab, Biological therapies, Treatment.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a widespread and debilitating dermatological disease, with a prevalence of up to 20% of the general population at some point in their lives. Women are affected twice as often as men, particularly in their 30s. This disease is the result of various factors and usually occurs

without any specific stimulus, although some aggravating factors, such as stress and infections, can increase the activity of the disease. It is a condition that can persist for years, causing a significant impact on patients' quality of life, impairing sleep, emotional well-being and professional and academic performance, mainly due to pain and itching. Despite impacting a substantial portion of the population, available treatments still have limited efficacy, with around a third of patients not responding satisfactorily to existing therapies (Casale *et al.,* 2023; Wang; Chan, 2020; Kolhir *et al.*, 2022).

The main manifestations of UCE are pruritic papules and angioedema, present for more than six weeks, with recurrent and migratory characteristics. These manifestations result from vasodilation, increased vascular permeability and activation of sensory nerves, triggered by the degranulation of mast cells, which release vasoactive mediators, mainly histamine. In addition to mast cells, the affected lesions show high infiltration of basophils, eosinophils, monocytes, lymphocytes and neutrophils, similar to a late occurrence caused by exogenous allergens, bringing about a predominantly Th2 profile response. Currently, the main therapeutic option is the use of second-generation antihistamines; however, around 61% of patients are refractory to this treatment (Wang; Chan, 2020; Kaplan *et al.*, 2022).

The aim of treating UCE is to eliminate the symptoms caused by papules and angioedema. Given the limited clinical impact of antihistamines, omalizumab has emerged as a promising alternative. It is a monoclonal antibody that binds to immunoglobulin E (IgE), preventing its interaction with high brightness receptors (FceRI) on antigen-presenting cells and mast cells. This action reduces the release of inflammatory mediators and, consequently, the activation of allergic pathways, providing symptomatic relief. Although omalizumab is considered effective and well tolerated in all age groups, there is still no consensus on its use and management in children and adolescents (Asero, 2021; Wang; Chan, 2020).

Therefore, the use of alternative therapies, such as biological ones, is still a relatively recent strategy, the implementation of which is predominantly based on research carried out on adult populations. Although progress has been made in controlling chronic spontaneous urticaria, important gaps remain, especially in understanding the mechanisms of action of these therapies and their applicability in specific subgroups, such as children, the elderly and patients with comorbidities (Casale *et al.,* 2023). Thus, it is essential to expand studies investigating recent advances in the use of biologics, analyzing not only their clinical efficacy, but also aspects such as safety, cost-effectiveness and impact on patients' quality of life (Abuzakouk *et al.,* 2020). Thus, the aim of this study is to examine the role of biologics, with a focus on omalizumab and other off-label biologic therapies, in the management of chronic spontaneous urticaria, discussing their mechanisms of action, efficacy, biomarkers of response and prospects for future treatments.

METHODOLOGY

This is a narrative literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question "What are the recent advances in the use of biologics for the treatment of chronic spontaneous urticaria and how do these therapies influence disease control and patients' quality of life?". The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combina-

International Journal of Health Science ISSN 2764-0159 DOI https://doi.org/10.22533/at.ed.159542514013

tion with the Boolean terms "AND" and "OR", using the following search strategy: (urticaria) AND (treatment) AND ((monoclonal antibody) OR (omalizumab) OR (tezepelumab) OR (biologic treatment)). From this search, 1,457 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in English, published between 2020 and 2024 (last 5 years) and which addressed the themes proposed for this research, review-type studies, meta-analysis, observational studies and experimental studies. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, 18 articles were selected from the PubMed database to make up the collection of this study.

DISCUSSION

Omalizumab, a humanized anti-IgE monoclonal antibody, revolutionized the treatment of chronic spontaneous urticaria (CSU) when it was approved in 2014 for patients who accidentally failed to respond to antihistamines. This innovative therapy has demonstrated significant efficacy in controlled clinical trials and real-world studies, relieving the persistent symptoms of the disease, such as intense pruritus and angioedema, and promoting consistent improvements in patients' quality of life. In addition to relieving physical symptoms, omalizumab has been shown to be effective in reducing the emotional impact of SCU, which often affects patients' mental health due to the unpredictability and chronicity of the condition (Metz *et al.,* 2020; Coşansu *et al.,* 2022).

The therapeutic efficacy of omalizumab is deeply rooted in its mechanism of action, which involves a separate binding to immunoglobulin E (IgE), reducing its free levels by more than 90%. This results in a significant decrease in the expression of the high-layer receptor for IgE (FcεRI) on mast cells and basophils, key cells in mediating the inflammation characteristic of UCE (Rauber *et al.,*2020). This direct modulation reduces the release of inflammatory mediators, relieving the symptoms of the disease. However, around 30% of patients do not achieve adequate symptom control with the licensed doses of 150 mg or 300 mg, even after six months of treatment. These data emphasize the importance of personalized therapeutic approaches, which take into account the individual variability and specific clinical needs of each patient (Metz *et al.,* 2020; Yosipovitch *et al.,* 2023).

Given the limitations of standard doses, studies have investigated adjustments to the dosage of omalizumab as an alternative to improve therapeutic results in refractory patients (Calzari *et al.,* 2024). Increased doses, such as 450 mg or 600 mg per month, have shown promising results, allowing effective control of the disease in up to 60% of patients who show an insufficient response to standard doses. This strategy has been particularly effective in individuals with specific clinical characteristics, such as high body mass index (BMI) or limited total IgE levels. This evidence reinforces the importance of individualizing treatments, adjusting therapeutic approaches to the specific immunological and metabolic characteristics of each patient (Coşansu *et al.,* 2022; Russo *et al.,* 2022).

The efficacy of omalizumab in UCE is often assessed using standardized tools, such as the Urticaria Activity Score over 7 days (UAS7), which measures disease activity over seven days (Manzoor *et al.,* 2022). A score ≤ 6 is indicative of complete control of urticaria, while values higher than 16, even after several doses of 300 mg, indicate an unsatisfactory response. Another widely used metric is the Urticaria Control Test (UCT), in which values

≥ 12 reflect a controlled disease. These standardized tools allow precise monitoring of the response to treatment, helping to identify patients who may benefit from adjustments to the dose or frequency of administration (Metz *et al.,* 2020; Traidl and Wedi, 2023).

In addition to controlling dermatological symptoms, omalizumab has also shown important benefits in emotional aspects, such as reducing anxiety and depression. These conditions, frequently observed in patients with UCE, were assessed using the Hospital Anxiety and Depression Scale (HADS), which revealed significant improvements during treatment. In parallel, quality of life scores, such as the Dermatology Life Quality Index (DLQI), also made notable advances, highlighting the positive impact of omalizumab on patients' mental health and general well-being. These results highlight the crucial role of omalizumab in the integrated management of SCU, addressing both the physical symptoms and the psychosocial consequences of the disease (Diluvio *et al.,* 2020).

Despite the substantial advances made with the use of omalizumab, challenges remain, especially in identifying predictive biomarkers of treatment response (Sánchez-Borges *et al.,* 2021). Factors such as high total IgE levels and BMI have been associated with different response patterns, but the results between studies are still inconsistent. In addition, the lack of standardization in the definition of response to treatment compromises the comparability of data between studies. New studies are needed to explore more flexible dose regimens and investigate new therapies, such as ligelizumab and BTK (Bruton Tyrosine Kinase) inhibitors, which offer promise for refractory patients (Wedi; Traidl, 2021). These approaches could broaden therapeutic options and improve accessibility and efficacy in the management of SCU (Gooderham *et al.,* 2024; Maurer *et al.,* 2022).

FINAL CONSIDERATIONS

UCE is a dermatological disease that affects around 20% of the population and has a significant impact on quality of life due to the limited effectiveness of the treatments currently available. The therapeutic goal is to eliminate the symptoms of papules and angioedema, but given the limitations of antihistamines, the use of omalizumab, a monoclonal antibody that binds to immunoglobulin E (IgE), has been highlighted as an alternative for patients refractory to conventional treatment. Approved since 2014, omalizumab has shown moderate efficacy with standard doses of 150 mg and 300 mg, leading to research into higher dosages, such as 450 mg or 600 mg, which show promising results, with up to 60% of patients responding to treatment. However, efficacy varies according to individual patient factors, such as high body mass index (BMI) and low levels of total IgE. Studies are still needed to fully elucidate its mechanism of action in UCE and to develop an individualized therapy algorithm, taking into account the factors that influence clinical results and increase treatment efficacy and safety.

REFERENCES

ABUZAKOUK, Mohamed *et al.* Efficacy and Safety of Biologic Agents in Chronic Urticaria, Asthma and Atopic Dermatitis - A Real-life Experience. **The Open Respiratory Medicine Journal**, v. 14, p. 99 - 106, 2020.

ASERO, Riccardo. Omalizumab in severe chronic urticaria: are slow and non-responders different. **Eur Ann Allergy Clin Immunol**, v. 53, n. 6, p. 263-266, 2021.

CALZARI, Paolo *et al.* Omalizumab for the Treatment of Chronic Spontaneous Urticaria in Adults and Adolescents: An Eight-Year Real-Life Experience. **Journal of Clinical Medicine**, v. 13, n. 18, p. 5610, 2024.

CASALE, Thomas B, *et al.* Omalizumab for Patients with Chronic Spontaneous Urticaria: A Narrative Review of Current Status. **Dermatology and Therapy**, v. 13, n. 11, p. 2573-2588, 2023.

COŞANSU, Nur Cihan; KARA, Rabia Öztas; YALDIZ, Mahizer; DIKICIER, Bahar Sevimli. New markers to predict the response to omalizumab in chronic spontaneous urticaria. **Dermatologic Therapy**, v. 35, n. 8, p. e15589, 2022.

DILUVIO, Laura *et al.* Improving of psychological status and inflammatory biomarkers during omalizumab for chronic spontaneous urticaria. **Future Science OA**, v. 6, n. 9, p. FSO618, 2020.

GOODERHAM, Melinda J; KWATRA, Shawn G; GENG, Bob. From Research to Practice: The Latest Data on Evolving Treatments for Chronic Spontaneous Urticaria. **Journal of drugs in dermatology: JDD**, v. 23, n. 9, p. 795-806, 2024.

KAPLAN, Allen *et al.* Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances. **Allergy**, v. 78, n. 2, p 389-401, 2022.

KOLKHIR, Pavel *et al.* Urticaria. **Nature Reviews Disease Primers**, v. 8, n. 1, p. 1–22, 2022.

MANZOOR, Humayun *et al.* Efficacy of different dosing regimens of IgE targeted biologic omalizumab for chronic spontaneous urticaria in adult and pediatric populations: a meta-analysis. **In: Healthcare**. MDPI, p. 2579, 2022.

METZ, Martin; VADASZ, Zahava; KOCATURK, Emek; GIMÉNEZ-ARNAU, Ana K. Omalizumab Updosing in Chronic Spontaneous Urticaria: an Overview of Real-World Evidence. **Clinical Reviews in Allergy & Immunology**, v. 59, n. 1, p. 38–45, 2020.

RAUBER, M. M, *et al*. Omalizumab response correlates with reduced IFN-γ-, IL-10-and IL-31-secreting cells in chronic spontaneous urticaria. **Journal of the European Academy of Dermatology and Venereology**, v. 34, n. 9, p. 2078-2085, 2020.

RUSSO, Irene; CAZZOLLA, Sara; PAMPALONI, Francesca; ALAIBAC, Mauro; Omalizumab for the Treatment of Chronic Spontaneous Urticaria: Association Between Body Mass Index and Outcome. **Dermatology Practical Conceptual**, v. 12, n. 4, 2022.

SÁNCHEZ-BORGES, Mario *et al.* The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations. **World Allergy Organization Journal**, v. 14, n. 6, 100546, 2021.

TRAIDL, Stephan; WEDI, Bettina. Prospective, monocentric, observational study of the long-term effectiveness of omalizumab in chronic urticaria. **Allergologie Select**, v. 7, p. 1, 2023.

WANG, Evelyn A; CHAN, Sanny K. Chronic urticaria in children: An update on diagnosis and treatment. **Current Allergy and Asthma Reports**, v. 20, p. 1-7, 2020.

WEDI, Bettina; TRAIDI, Stephan. Anti-IgE for the Treatment of Chronic Urticaria. **ImmunoTargets and Therapy**, p. 27-45, 2021.

YOSIPOVITCH, Gil; SOARES, Georgia B.; MAHMOUD, Omar. Current and Emerging Therapies for Chronic Spontaneous Urticaria: A Narrative Review. **Dermatology and Therapy**, v. 13, n. 8, p. 1647–1660, 2023.