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Chronic urticaria: Pharmacological treatment

Urticária crônica: Tratamento farmacológico

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ABSTRACT

Introduction: Chronic urticaria is a skin condition characterized by recurrent episodes of itching and rashes, which persist for more than six weeks. Its effective management is essential to improve the quality of life of patients. This study aims to evaluate best practices in the management of chronic urticaria. Objectives: To evaluate the most effective treatment options available for patients with chronic urticaria. Methodology: A literature review was conducted, including clinical studies and recent medical guidelines. Treatment options, diagnosis, safety and efficacy of medications, and management strategies in different age groups were analyzed. Results: The results of this review highlight that non-sedating H1 antihistamines are the first line of treatment for chronic urticaria. In cases of treatment resistance, other options such as systemic corticosteroids and immunosuppressants may be considered, albeit with caution due to potential side effects. In elderly patients, hepatic and renal function should be considered when choosing drugs. In addition, identifying possible underlying causes is crucial for the effective management of chronic urticaria. Conclusion: The management of chronic urticaria requires a personalized approach based on the assessment of the patient's needs, considering age, comorbidities, and drug safety. Identification and treatment of the underlying causes, where possible, are essential. With current guidelines and therapeutic options, it is possible to significantly improve the quality of life of patients with chronic urticaria.

Keywords: Chronic urticaria, Pharmacological treatment,Itch.

1 INTRODUCTION

Chronic urticaria is characterized by the presence of urticaria for a period of more than 6 weeks and that manifests itself through raised, reddish and itchy plaques, as well as angioedema (localized edema) that can appear anywhere in the body. Edema of the superficial dermis is called urticaria, and edema of the deep dermis, subcutaneous tissue and gastrointestinal tract is called angioedema. In most cases it is a self-limiting disease, lasting from 1 to 5 years, however, in about 20% of the affected population, urticaria lasts more than 5 years. Urticaria can be divided into chronic induced urticaria, when it is possible to identify an external triggering factor, or chronic spontaneous urticaria, when no specific cause can be defined (GENN; ELIAN, 2022).

Regarding the existing division, induced chronic urticaria is identified by the clinical history of pruritus that arises after contact/use of some substance, which usually persists for a defined time and when biopsied, no cellular infiltrate is found. Chronic spontaneous urticaria, on the other hand, appears independently of any stimulus, although there are intrinsic circumstances that worsen the condition. (SAINI; KAPLAN, 2018)

Histological analysis of lesions in patients with chronic urticaria can demonstrate varied findings, including mononuclear cells (CD4+, Th1 and Th2 lymphocytes), eosinophils, neutrophils, basophils, mast cells, and activated macrophages. In addition, some biopsies may show edema with little cellular infiltrate, while others may show "perivasculitis," since there is a mononuclear infiltrate that does not damage the vessel wall. (GREENBERGER, 2014)

The pathophysiology of the disease is still not well understood, however, it is proven that mast cell degranulation and the release of inflammatory factors, such as histamine, leukotrienes and other products derived from arachidonic acid, are closely related to urticaria. The physical manifestation of pruritus may be related to factors released by mast cells that cause increased vascular permeability, sensory nerve activation, extravasation, and recruitment of circulating inflammatory cells. In some patients, physical stimuli such as pressure, heat, or cold cause hives that tend to become chronic. Systemic diseases have been cited as an uncommon cause of urticaria, and among the associated comorbidities, the main one is Hashimoto's thyroiditis. (SCHAEFER, 2017; ELIEH-ALI-KOMI et al., 2023)

Regarding chronic spontaneous urticaria, studies suggest that psychological factors such as stress can act as a trigger for the onset of this condition. On the other hand, the itching felt by the individual can lead to stress, making the condition even worse. In this sense, it is worth

mentioning the negative influence that urticaria has on the patient's life, directly impacting the individual's quality of life and their cognitive, social, emotional and physical functioning. (OGRACZYK-PIOTROWSKA et al., 2018)

Still in relation to the mechanism of chronic urticaria, about 35 to 45% have an autoimmune origin, in which the body itself leads to the activation of cells to release histamine. Among the factors implicated in the appearance of induced urticaria, it is possible to mention some drugs of very common use, such as dipyrone and other non-steroidal anti-inflammatory drugs (NSAIDs), opioids, angiotensin-converting enzyme (ACE) inhibitors and alcohol. Rarer causes are infection with parasites and even Helicobacter pylori. Some infectious agents such as hepatitis A and B viruses, herpes simplex viruses and mycoplasma species have also been mentioned. There is little evidence that chronic urticaria can be a sign of occult internal malignancy. (SCHAEFER, 2017)

The diagnosis of urticaria is clinical, based on the patient's history. In order to rule out other comorbidities, a laboratory investigation can be performed, including tests such as blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), as well as thyroid hormone values. In the literature, there are still disagreements about the tests required for diagnosis. After diagnosis, scores such as the Urticaria Activity Score and the Quality of Life Questionnaire for Chronic Urticaria are used to assess symptom control and treatment effectiveness. (COSTA; GONÇALO, 2016)

In the treatment of urticaria, they also include specific recommendations for certain populations, such as children and the elderly. In chronic spontaneous urticaria (CSU) in children, the causes are similar to those in adults, but there is no predominance in females. Treatment begins with non-sedating H1 blockers, with dose adjustment based on the child's weight after 2 weeks if necessary. Systemic corticosteroids can be used for a maximum of 10 days in case of exacerbation, but with caution due to possible adverse effects, especially in children. The third treatment option includes Omalizumab, cyclosporine, or Montelukast, with cyclosporine requiring consideration due to side effects. Omalizumab is approved for patients 12 years of age and older, but smaller studies show its efficacy and safety in younger children. (ANA CÉLIA COSTA et al., 2016)

In geriatric patients (65 years of age and older), it is important to follow the latest European recommendations. However, this group often has multiple comorbidities and uses multiple medications, which requires consideration of potential drug interactions, including those with cyclosporine. Additionally, it is critical to assess kidney and liver function, as this can affect the effectiveness and safety of medications. It is important to emphasize that the use of cyclosporine

and systemic corticosteroids may potentiate adverse effects, especially in elderly patients with hypertension and impaired renal function. (ANA CÉLIA COSTA et al., 2016)

Because it is a psychologically debilitating disease with a high socioeconomic impact, its correct identification and commitment to therapeutic strategies aimed at the total control of the symptomatology is of paramount importance. Understanding this condition is important to provide patients with effective treatment, symptom relief, and improved quality of life.

2 OBJECTIVE

This study aims to address the therapeutic management of patients with chronic urticaria and the various nuances involved, since it is a condition characterized by significant impairment of quality of life in several spheres.

3 MATERIALS AND METHODS

The present study is an integrative literature review that enables the search, critical evaluation and synthesis of available evidence on the investigated topic. In the first stage, the following guiding question was asked: "How to perform the therapeutic management of chronic urticaria?".

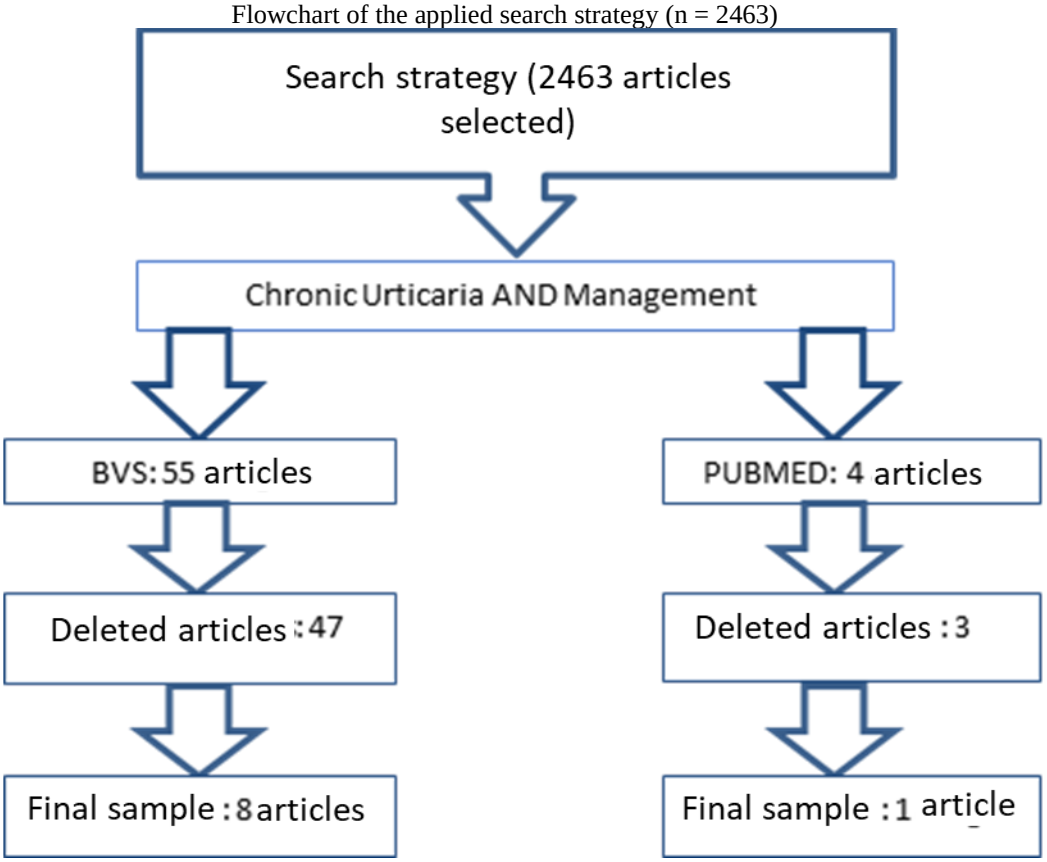
Then, in the second stage, in October 2023, the scientific search was carried out through the PubMed and VHL platforms, using the following descriptors indexed in the Health Sciences Descriptors (DeCS): "Chronic urticaria" and "Management'', which were gathered using the Boolean descriptor AND.

Regarding the inclusion criteria for the selection of articles, the following were established: randomized clinical trials published in the last five years, available as full text and in English or Portuguese.

Initially, 2463 studies were found based on the use of the descriptors in the databases, 184 in PubMed, 2165 in Medline, 32 in Latin American and Caribbean Health Sciences Literature (LILACS), 38 in the Spanish Bibliographic Index in Health Sciences (IBECS), 25 in the Index Medicus for the Western Pacific (WPRIM), 6 in the Bibliographía Nacional en Ciencias de la Salud Argentina (BINACIS); 5 in HomeoIndex – Homeopathy; 2 at the National Center for Information on Medical Sciences of Cuba (CUMED); 2 at the Peruvian Network of Libraries in Health-LIPECS; 1 at BIGG - GRADE guides; 1 at The Regional Database of Health Technology Assessment Reports of the Americas (BRISA); 1 at the RDSM Relational Database Service Manager (RDSM) and 1 at the São Paulo State Department of Health. After applying the inclusion

and exclusion criteria, 53 studies were selected; These were screened considering the reading of the title and keywords, and 19 studies were considered in the next stage of selection. There was the exclusion of 1 work due to duplicity, leaving 18 to be read. Of the 18 studies, 14 underwent a full analysis and 9 investigations made up the final sample.

Flowchart of the applied search strategy (n = 2463)



Finally, a data collection form was used for the critical analysis of the studies, consisting of the following information: title; Authors; year; place of execution of the study; sample; goal; design and main results. The selection of articles was carried out independently by two authors and there was no disagreement regarding the selected works.

4 RESULTS

The studies analyzed were published between 2018 and 2023 and conducted in Canada, Switzerland, Colombia, Spain, Germany, China, Japan, Iran, the Netherlands, and Denmark. Regarding the methodological approach, the studies were double-blind randomized clinical trials (n=2; 22%); In a non-randomized clinical trial (n=2; 22%) and a retrospective cohort (n=4; 45%) and a prospective cohort (n=1, 11%), the studies were described and listed in a demonstration table (Chart 1).

Table 1 – Characteristics of the selected studies. (n=9).

Author and year	Outline	Objective	Sample & Scenario	Main results
Alireza firooz *et al.*, 2018	Retrospective cohort	To evaluate the practice of Iranian dermatologists and the management of patients with cholinergic urticaria.	35 Dermatologists and 443 Iranian patients. The patients had cholinergic urticaria.	Monotherapy with moderate- to high-dose 2nd generation antihistamines as first-line treatment was used with high frequency. Topical treatments with topical antihistamines and leukotriene antagonists were prescribed by only 3% of dermatologists.
Das *et al.*, 2021	Double-blind randomized clinical trial	To evaluate and compare the effectiveness and safety of bepostatin and levocetirizine for the treatment and control of cholinergic urticaria.	30 patients on bepostatin and 29 patients on levocetirizine.	Bepostatin offers a therapeutic effect similar to levocetirizine, but with reduced side effects.
Dekkers *et al.*, 2021	Retrospective cohort	To investigate the effectiveness and safety of omalizumab in pediatric patients with cholinergic urticaria.	Patients admitted to Wilhermina Children's Hospital in the Netherlands who were diagnosed with cholinergic urticaria and underwent omalizumab before the age of 18 years.	Omalizumab showed high efficacy and safety in pediatric patients with cholinergic urticaria.
García-Gómez *et al.*, 2022	Retrospective cohort	To describe the characteristics and clinical response to omalizumab treatment in patients with cholinergic urticaria in five hospitals in Colombia.	123 patients admitted to five hospitals in Colombia diagnosed with cholinergic urticaria.	No serious adverse events were reported. Headaches, myalgias, and arthralgias were the most common collaterals observed.
Ghazanfar; Holm; Thomsen, 2018	Non-randomized clinical trial	To examine the efficacy of omalizumab on symptoms and quality of life in patients with cholinergic urticaria. To identify possible factors associated with the positive response to omalizumab use.	6 months of omalizumab 300mg/day every 4 weeks among patients with cholinergic urticaria in a dermatological university hospital.	Omalizumab is highly effective for cases refractory to antihistamines.
Hide *et al.*, 2019	Non-randomized clinical trial	To investigate the long-term efficacy and safety of rupatadine in the management of pruritus in Japanese adolescents and adults.	Japanese adolescent and adult patients received the medication for 52 weeks for the study.	The study showed short- and long-term benefits in the control of patients with chronic urticaria, dermatitis and pruritus.

Pivneva *et al.*, 2022	Retrospective cohort	Develop a predictive model for clinical remission by assessing clinical and demographic characteristics using a machine learning methodology.	102 Million people receiving treatment in more than 700 hospitals and 7000 clinics in the United States.	Complex interactions between variables, which are difficult to identify and interpret through clinical judgment alone, have been observed.
Rodriguez *et al.*, 2020	Double-blind randomized clinical trial	To evaluate the feasibility of long-term use of bilastine in children 6-11 years of age with cholinergic urticaria.	Children 6-11 years of age with chronic urticaria receiving 10mg of bilastine daily or placebo for 12 weeks.	Pharmacokinetics and therapeutic safety make it possible to use a daily dose of 10mg of bilastine in children with cholinergic urticaria.
Puga *et al.*, 2023	Prospective cohort	To understand the profile of patients with cholinergic urticaria, clinical management and the impact on quality of life in Spain.	39 hospitals and 42 researchers (21 dermatologists and 21 allergists). All patients in the study were over 18 years of age at the time of data collection and had cholinergic urticaria.	The impairment of the quality of life of patients with cholinergic urticaria is important. Thus, the physicians in charge should intensify the therapies aimed at improving the quality of life of these patients.

5 DISCUSSION

Chronic urticaria is a challenging dermatological condition characterized by the presence of raised, reddish, and extremely itchy plaques on the skin, this chronic condition has a significant impact on the quality of life of patients. Unlike acute urticaria, which typically resolves in short periods, chronic urticaria is characterized by recurrent episodes that persist for more than six weeks and can last for months or years (DEKKERS et al., 2021).

Chronic urticaria is a debilitating condition with considerable impairment to the patient's quality of life. Most patients seek treatment for their symptoms, but many face persistent challenges in seeking complete relief. Since it is a condition that plays an important role in individual well-being, a holistic approach is welcome. Healthcare professionals, particularly dermatologists, play a crucial role in the diagnosis and treatment of chronic urticaria. However, dermatologists' perceptions regarding treatment guidelines and the use of specific therapies vary, which may have an impact on the uniformity of management of chronic urticaria. Therefore, it is essential to have clear and direct guidelines about the workup for chronic urticaria, improving the diagnosis and intervention of this challenging pathology. (ALIREZA FIROOZ et al., 2018)

The approach to chronic urticaria can be carried out in several ways. An innovative way to predict the clinical remission of pathology is by applying machine learning techniques. The use of Random Survival Forests (RSF) in real-world data analysis offers a promising way to predict

clinical remission of chronic urticaria. This innovative approach allows clinicians to identify risk factors, patterns, and variables that may influence remission, which can be valuable in guiding treatment decisions. This tool is also effective in identifying subgroups of patients with a higher likelihood or need for specific interventions (PIVNEVA et al., 2022).

The approach to chronic urticaria should be personalized in relation to diagnosis and treatment. Doctors often face difficulties in managing chronic urticaria due to its recurrent nature and a lack of complete understanding of its causes. Thus, in addition to implementing clear and objective guidelines about the condition, as well as continuing education, it is important to inform patients about their condition, which can improve self-care and treatment adherence. (PUGA et al., 2023)

Pharmacological treatment of chronic urticaria seeks to relieve symptoms, particularly severe itching and rash, and may vary according to the severity of the condition and the patient's individual response The first line of treatment usually involves the use of second-generation antihistamines such as cetirizine, loratadine and fexofenadine. These medications block the action of histamine, a substance released into the body that triggers the symptoms of hives. While many patients respond well to these antihistamines, others may require higher doses or a combination of different medications to achieve complete symptom relief. (DAS et al., 2021).

For patients with chronic urticaria refractory to second-generation antihistamines, other pharmacological options may be considered. Corticosteroids, such as prednisone, are reserved for short-term treatment of severe exacerbations because of the side effects associated with long-term use. In addition, immunosuppressants can be prescribed in severe and resistant cases, but require careful monitoring because they present more risks associated with use (PUGA et al., 2023).

A newer and more promising therapy for chronic urticaria is omalizumab, a monoclonal antibody that works to inhibit IgE, a protein involved in allergic reactions. Omalizumab has been shown to be effective in reducing the symptoms of chronic urticaria in patients who have not responded adequately to antihistamines. However, its high cost may limit access for some patients (GARCÍA-GÓMEZ et al., 2022).

Patient education about the condition and its treatment is also important, as well as the need for regular monitoring to adjust therapy as needed. Assessment of response to treatment and identification of potential triggers are key parts of the management of chronic urticaria. The pharmacological treatment of chronic urticaria is multifaceted and must be tailored to the individual needs of each patient. The availability of different therapeutic options offers hope for those suffering from this debilitating condition, but challenges doctors to find the most effective

approach for each case. Ongoing research in this field promises new advances in the treatment of chronic urticaria and improving the quality of life for affected patients. (PUGA et al., 2023)

Regarding the pharmacological intervention of chronic urticaria, several options are viable. The use of antihistamines, such as levocetirizine and bepostatin, is a viable option. Both drugs are helpful in reducing the symptoms of the disease, thereby providing relief to patients. Both medications showed significant improvements in urticaria symptom severity, as evidenced by decreased UAS Activity Score 7. In addition, the study did not identify significant differences in efficacy between levocetirizine and bepotastine, suggesting that both drugs are viable choices for the treatment of chronic urticaria. However, levocetirizine had a greater number of side effects, mainly somnolence, than bepostatin. This may influence long-term tolerability and therapeutic adherence. (DAS et al., 2021).

Another viable antihistamine for the treatment of chronic urticaria is rupatadine. This medication shows substantial improvements in reducing the severity and associated symptoms, providing relief to patients for prolonged periods. In addition, the medication is usually well-tolerated and safe, offering few adverse events (HIDE et al., 2019).

Bilastine, a 2nd generation antihistamine, is also a viable option not only for chronic urticaria but also for allergic rhinoconjunctivitis. Bialstin is well tolerated and has a safe pharmacokinetic profile also in children, and is therefore a viable option in this age group (RODRÍGUEZ et al., 2020).

As we can see, several pharmacological options are viable. To choose one, the age group, concomitant use of other medications, and the degree of severity of cholinergic urticaria should be evaluated. In more severe cases, 2nd generation antihistamines are often not effective in managing the condition. For these situations, anti-IgE immunotherapy has been developed, with omalizumab being the main representative. The medication has been shown to be effective in relieving symptoms and improving quality of life in patients with chronic urticaria. The reduction in UAS7 (Urticaria Activity Score 7) reflects the decreased severity of urticaria symptoms, indicating a positive response to omalizumab treatment. In addition, the drug was well tolerated, with few significant adverse events reported. This is particularly relevant for clinicians and patients around the world as new effective therapeutic options for the management of this challenging skin condition are developed. (GARCÍA-GÓMEZ et al., 2022)

Other studies evaluating the efficacy of omalizumab in the treatment of chronic urticaria were selected for this literature review. Other questionnaires were used to assess patients' quality of life and well-being. The assessment based on patients' perceptions, using instruments such as

the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), highlighted the importance of reducing symptoms in patients' lives and improving their quality of life. In addition, it presented a favorable safety profile, agreeing with the work of García-gómez, et al. (2022) (GHAZANFAR; HOLM; THOMSEN, 2018).

6 CONCLUSION

Chronic urticaria is an intriguing and challenging dermatological condition that affects the lives of countless individuals around the world. This study explored the various aspects of chronic urticaria, from its definition and classification to the complexities of its diagnosis and treatment. As we wrap up this review, it is evident that chronic urticaria is not just a skin condition, but an issue that can have a profound impact on patients' quality of life.

One of the key findings is that chronic urticaria is a heterogeneous and often complex condition with a diverse range of triggers, underlying mechanisms, and clinical presentations. Its chronic and recurrent nature makes treatment a constant challenge, which requires a personalized approach for each patient. Treatment often involves the use of antihistamines, corticosteroids, and, in more severe cases, immunosuppressants, although access to more advanced treatments, such as omalizumab, can provide significant relief.

Additionally, it is critical to recognize the psychological impact of chronic urticaria, which can lead to anxiety, depression, and a significant reduction in quality of life. Therefore, the multidisciplinary approach is crucial, including collaboration between dermatologists, allergists, and mental health professionals, to provide the best care to patients.

However, research continues to advance, and new therapies are being investigated to treat chronic urticaria, promising relief for those suffering from this condition. As the understanding of the pathogenesis of chronic urticaria evolves, new therapeutic approaches may be developed, providing hope to patients struggling with the debilitating symptoms of chronic urticaria.

Finally, chronic urticaria is a complex condition that requires a multidisciplinary approach to diagnosis, treatment, and supportive care. With a continued focus on research, interdisciplinary collaboration, and improved access to effective therapies, it is possible to improve the quality of life for patients facing the challenges of chronic urticaria.

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