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The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations

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ABSTRACT

This is Part 2 of an updated follow-up review of the World Allergy Organization (WAO) position paper on the diagnosis and treatment of urticaria and angioedema. Since that document was published, new advances in the understanding of the pathogenesis of chronic urticaria, and greater experience with the use of biologics in patients with severe refractory disease, mainly omalizumab, have been gained. For these reasons, WAO decided to initiate an update targeted to general practitioners around the world, incorporating the most recent information on epidemiology, immunopathogenesis, comorbidities, quality of life, clinical case presentations, and the management of chronic spontaneous and chronic inducible urticaria, and urticaria in special situations such as childhood and pregnancy. A special task force of WAO experts was invited to write the different sections of the manuscript, and the final document was approved by the WAO Board of Directors. This paper is not intended to be a substitute for current national and international guidelines on the management of urticaria and angioedema, but to provide an updated simplified guidance for physicians around the world who have to manage patients with this common ailment.

Keywords: Angioedema, Chronic inducible urticaria, Chronic spontaneous urticaria, Omalizumab, Treatment, Urticaria

INTRODUCTION

Chronic spontaneous urticaria (CSU) is clinically manifested as wheals and/or angioedema (AE) lasting for more than 6 weeks, affecting all age groups, and observed more often in females. Its prevalence has been estimated in 1–2%.[1] This condition compromises daily life,[2] and is associated with several comorbidities, both physical and psychological, such as depression and anxiety.[3] There is also an important economic impact of the disease which has been calculated in more than 200 million $ per year in the United States, especially due to medication costs, and work absenteeism.[4]

Recent investigations have advanced the knowledge on the immunological mechanisms of CSU and AE and have opened opportunities to postulate new therapies directed to specific molecular targets for this disease.

In 2012 WAO published a position paper on the diagnosis and treatment of urticaria with a global

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vision.[5] Since then, greater experience with the use of biologics, mainly omalizumab, in patients with severe disease has been acquired. WAO decided to initiate an updated review of that paper targeted to general practitioners around the world, incorporating the most recent information on epidemiology, immunopathogenesis, comorbidities, quality of life, clinical case presentations, and the management of CSU and chronic inducible urticaria (CIndU), including urticaria in special situations such as childhood and pregnancy. This update is a summary of the most current information on urticaria and angioedema and was developed to offer guidance to general practitioners worldwide who must deal with this disease, although it is not intended to be a substitute for national and international guidelines which are currently in use.

THERAPEUTICS AND INTEGRAL MANAGEMENT OF CHRONIC SPONTANEOUS URTICARIA AND CHRONIC INDUCIBLE URTICARIA

Pharmacological treatment

The treatment of chronic urticaria has been delineated in various national and international guidelines that proposed a stepwise protocol of therapy based on symptom severity and response to the medication.[5–8] There are some differences between the International Guidelines and the North American Guidelines.[9]

Antihistamines

Nonsedating (second generation) H1 antihistamines (NS AHs) are recommended in both the International and North American Practice Parameters as the first line treatment for CU due to their relative efficacy and safety. However, the North American paper includes first generation antihistamines in steps 2 and 3.[7] When patients do not respond to approved doses of NS AHs, doses can be increased up to 4 times (step 2) to improve efficacy without compromising safety.[6] (Fig. S1 in supplementary archive)

The utilization of combinations of AHS does not seem to induce better therapeutic effects than increasing the dose of a single NS AH.[10] Even at increased doses AHs may not be effective in 40–45% of patients with CU.[11,12] These patients with CU refractory to AHs are candidates to receive additional treatment (Steps 3 and 4).

Histamine H2 blockers do not seem to improve urticaria and have been deleted from the EAACI/GA2LEN/EDF/WAO International Guidelines, but are still recommended in the North American Guidelines.[6,7]

Omalizumab

The only biological medication currently approved for the treatment of patients with AH-refractory moderate to severe CSU is Omalizumab (OMA), a monoclonal antibody (mAb) directed to the Cϵ3 domain of human IgE heavy chain, the same site that binds to Fc receptors on mast cells and basophils. Efficacy and safety of OMA in CSU have been demonstrated in double-blind placebo controlled studies,[13] and confirmed through meta-analysis.[14] Dosing recommended for omalizumab is 150 mg or 300 mg q4 weeks.

In addition to binding to serum IgE which results in a decrease of total and autoantigen-specific IgE

➢ Reduction of serum IgE levels
➢ Dissociation of IgE-FcεRI binding
➢ Reduction of IgE receptor numbers on mast cell and basophil membranes
➢ Reduction of mast cell/basophil degranulation
➢ Reversion of basopenia and improvement of IgE receptor function in basophils
➢ Reduction in anti-FcεRI and anti-IgE IgG autoantibody activity
➢ Reduction in autoantigen IgE autoatibodies

Table 1. Mechanisms of action of Omalizumab in Chronic Spontaneous Urticaria

Strategy	Potential targets	Drugs
Drugs that inhibit effects of activation signals and mast cell numbers	IgE	Ligelizumab
	IL-25	–
	IL-33	–
	TSLP	–
	Stem cell factor	–
	IL-4	Dupilumab
	IL-5	Mepolizumab, Benralizumab, Reslizumab
	C5a	–
	Mas-related G protein coupled receptor X2	–
Drugs that inhibit intracellular pathways of mast cell activation and degranulation	BTK inhibitors	Fenebrutinib, LOU064
	Syk inhibitors	GSK2646264
Drugs that silence mast cells through inhibitory receptors	Siglec-8	Anti-siglec-8 (antolimab)
	CD200R1	Anti-CD200R1 (Ly3454738)

Table 2. Future treatment options directed to the mast cell for patients with chronic urticaria

levels, other potential mechanisms of action to explain OMA efficacy in CSU have been proposed[15] (Table 1).

Although a significant number of patients respond rapidly to OMA (fast responders, in 4–6 weeks), some of them show slow responses (12–16 weeks). The Urticaria Activity Score 7 (UAS7) is used to classify patients as complete responders, partial responders, or nonresponders.

Investigators have also been interested in the identification of biomarkers that help to predict the clinical response to OMA. For example, a positive basophil histamine release assay (BHRA), a positive autologous serum skin test (ASST), and the presence of eosinopenia would help to predict a slow or poor response, whereas higher expression of FcεRI, the absence of serum stimulating activity of expression of CD203c on basophils, higher levels of total serum IgE, a reduction of plasmatic D-dimer, and the reduction of serum IL-31 levels could predict a faster or favorable response.[16]

Cyclosporin-A

The second alternative drug that has been shown to be effective for patients with treatment-resistant CSU is cyclosporine-A (CsA).[17,18] CsA is an immunosuppressing drug that inhibits T helper cells by blocking the production of inflammatory cytokines. The complex between CsA and cyclophilin inhibits the phosphatase activity of calcineurin, down-regulating the transcription of cytokine genes (IL-2, IL-3, IL-4, TNF-α) and histamine, leukotriene, and prostaglandin release by mast cells and basophils *in vitro* and in vivo, and reducing serum levels of IL-2R, IL-5, and TNF-α.

In patients with antihistamine-resistant CU who fail to respond to OMA, 15–20% of the total, the most effective alternative medication is cyclosporine, as shown in double-blind, placebo-controlled studies.[17,18]

Response rate to a 4 mg/kg/day typical adult dose of cyclosporine in CSU is 60–70%.[19,20]

Subtype	Provoking agent	Prevalence in CIndU patients
Physical urticaria		
Symptomatic dermographism	Friction	Adults 50–78% Children 38%
Cold urticaria	Cold	Adults 8–37% Children 9–14%
Delayed pressure urticaria	Pressure	Adults 3–20% Children 3–9%
Solar urticaria	Light	Rare
Heat urticaria	Heat	Rare
Vibratory angioedema	Vibration	Rare
Other		
Cholinergic urticaria	Body warming	Adults 6–13% Children 19%
Contact urticaria	Contact with urticariogenic agent	Rare
Aquagenic urticaria	Water	Rare

Table 3. Subtypes of chronic inducible urticaria

However, other authors have observed that CsA controls CU only in 26–33% of patients.[17–21] A meta-analysis showed response rates of 54%, 66%, and 73% at 4, 8, and 12 weeks, respectively.[22] Calcineurin inhibitors are preferred by some physicians to treat severe CU, and as adjuvant therapy for difficult to control CSU.[23,24]

A retrospective parallel study from the United Kingdom observed a greater improvement in an Omalizumab-treated cohort than in the cyclosporine-treated cohort, based on clinician's opinions, dermatology life quality index (DLQI) scores, symptoms, and quality of life.[25]

Side effects (hypertension, nephrotoxicity, headache, nausea, abdominal pain, and infections) can occur; therefore; close monitoring every 6 weeks of blood pressure, renal function, and cyclosporine levels is recommended.[26]

Patients with positive basophil activation test (BAT) as well as those with a positive basophil histamine release assay (BHRA) respond better to CsA treatment.[27,28] Shorter duration of the disease and higher initial severity predict a successful response to treatment with CsA,[29] whereas baseline D-dimer levels show a highly significant negative correlation with the response to cyclosporine,[30] and D-dimer has been regarded as a good marker of disease activity useful to monitor the clinical response to CsA treatment[31] (Table 2). Nevertheless, a recent meta-analysis study by Kulthanan et al could not identify reliable practical laboratory biomarkers associated with favorable responses to CsA.[32]

Alternative non-validated treatments

Various additional drugs have been used in the past for the treatment of refractory CSU. These medications are not currently recommended because they have not been submitted to adequately controlled investigations and the information available comes from anecdotal observations, case reports, and small series of patients. However, some specialists continue to use them "off label" for patients with severe CU unresponsive to guideline-recommended therapies. Table 3 lists medications in that group that are not approved for CSU.

Biologicals and small molecules currently under investigation

Omalizumab is the only biological medication currently approved by regulatory agencies for the treatment of moderate to severe antihistamine

resistant CU. Nevertheless, other biologicals and small molecules are presently being investigated in patients with CU (Table 4).[16] Among others, IV immunoglobulins, TNF-α inhibitors (etanercept, adalimumab, infliximab),[16,33] IL-1 inhibitors (anakinra, rilonacept, canakinumab), anti-CD20 monoclonal antibody (rituximab),[34–38] anti-siglec-8 (AK002),[39] anti-TSLP (tezepelumab), anti-IL-4Rα (dupilumab,[40] pitrakinra, AMG-317, anti-IL-5/IL-5Rα (mepolizumab, reslizumab, benralizumab), anti-IL-13 (antukizumab, lebrikizumab, tralokinumab), anti-IgE (ligelizumab),[41] anti-NK-1R (atrepitant, tradipitant, serlopitant, AST-308, IMA-026, CNTO 5825, GSK679586, QAX576, anti-C5a (eculizumab), anti-β4integrin (natalizumab), anti-α4β7 integrin (vedolizumab), anti-β7 integrin (RhuMabβ7), T-cell costimulation modulator (abatacept), CRTh2 antagonist [AZD1981], BTK inhibitors (GDC0853, fenebrutinib, LOU064), Syk inhibitor (GSK2646264), anti-IL-33, anti-IL-25, anti-stem cell factor, anti-histamine HR4 (JNJ7777120).

Treatment of special conditions associated with urticaria

Some additional clinical disorders that are associated to urticarial lesions include the autoinflammatory syndromes and various forms of urticarial vasculitis. One of them, Schnitzler syndrome, is characterized by hyperostosis, lymphadenopathy, intermittent fever, and monoclonal IgM gammopathy. It is generally treated with second generation antihistamines and systemic glucocorticoids, and alternatively immunomodulators and immunosuppressors, for example, anti-IL-1 (anakinra or canakinumab).[42–44] Canakinumab also has been administered to patients with cryopirin-associated periodic syndrome,[45] and in urticarial vasculitis.[46]

Clinical cases: Chronic Inducible Urticaria

As its name implies, Inducible Chronic Urticaria (CIndU) is caused or induced by a specific environmental stimuli. The various forms of Chronic Inducible Urticaria occur after this specific and reproducible exposure. This set of conditions may also be referred to as Inducible Chronic Urticaria (CIndU) or simply Inducible Urticaria (ICU). In this manuscript we shall use the term Chronic Inducible Urticaria (CIndU).

CIndU can be caused by a variety of factors, which include cold and heat, delayed pressure, solar exposure, water exposure (aquagenic), vibratory urticaria, contact urticaria, and cholinergic urticaria (Table 5). A detailed history will cause the clinician to consider the diagnosis of CIndU, and there are specific tests available to help determine the cause of the individual patient's distress. The final diagnosis is based on the patient's history and the results of testing that is determined based on the patient's history. The tests shown below are confirmatory tests to be undertaken by a patient whose history has led the clinician to suspect a specific diagnosis.[48–51]

Cold Induced Urticaria

The patient in whom you suspect Cold Induced Urticaria. Patients with a history consistent with cold induced urticaria have a history of the appearance of wheals after exposure to cold or after cooling and rewarming of the skin. These wheals typically appear within minutes and last for

Anaphylaxis: Up to 80% of patients present urticaria as a clinical feature, and epinephrine is indicated when at least 2 organ systems are affected.
Viral Infections: May be associated with "urticaria multiforme". Self-limited condition that resolves as infection improves.
Serum sickness-like reactions (SSLR): Ecchymotic centers with large urticarial plaques. Hand and foot swelling may also be involved as well as fever, malaise, abdominal pain, headache, and diarrhea present 1–3 weeks after exposure to a certain drug.
Antihistamines, antipyretics, and in some cases oral steroids should be included in the management of SSLR and urticaria multiforme.

Table 4. Differential diagnosis of acute urticaria in pediatric patients

Primary immunodeficiency disease	Urticaria as reported in included articles	Number of reported cases	Prevalence of skin disorder (%)
Combined immunodeficiencies with associated or syndromic features			
Autosomal dominant hyper-IgE síndrome	Urticaria	13/82[82]	15.9%
Predominantly antibody deficiencies			
X-linked agammaglobulinemia	Urticaria	2/23[83]	8.7%
Common variable immunodeficiency	Urticaria	1/28[83]	3.6%
Selective IgA deficiency	Urticaria	5/23[84]	21.7%
	Allergic urticaria	4/123[85]	3.3%
	Chronic spontaneous urticaria	17/347[86]	4.9%
Diseases of immune dysregulation			
Autoinmune polyendocrinopathy candidiasis ectodermal dystrophy	Urticarial eruption	23/35 200[87]	8.6%
	Urticarial rash	2/22[88]	9.1%
Immunodysregulation polyendocrinopathy enteropathy X-linked sydrome			
Adenosine deaminase 2 deficiency	Urticaria-like rash	1/8[89]	12.5%
Congenital defects of phagocyte number or function			
Chronic granulomatous disease	Urticaria	1/48[90]	2.1%
Autoinflammatory disorders			
PLCG2 associated antibody deficiency and immune dysregulation	Cold urticaria	36/37[91]	100%
Muckle-Wells syndrome	Attacks of recurrent urticaria	2/6[92]	33.3%
	Urticaria	8/8[93]	100%
	Cold-induced urticaria	14/29[94]	48.3%
Neonatal-onset multisystem inflammatory disease	Urticaria	8/8[93]	100%
Complement deficiencies			
C2 deficiency	Chronic urticaria	2/47[95]	4.3%

Table 5. Manifestations of urticaria in primary immunodeficiencies diseases

approximately 1 h. Traditionally a provocation test is done by applying an ice cube to the volar surface of the forearm. This should be kept in contact with the patient's forearm for 5 min (monitor for patient tolerance). The test site should be evaluated 10 min after the removal of the ice cube. A wheal and flare reaction at the site of contact is considered positive. This is often associated with

itch and/or a burning sensation. If possible, threshold testing should be performed in patients with a positive test result.

If available, the use of a commercial TempTest device may be used to determine the temperature threshold of patients with Cold Induced Urticaria. The temperature threshold is the highest temperature that will induce a positive test reaction, and the patient can use this information to avoid situations where the temperature may be risky. If a TempTest device is not available, the ice cube test can be used to determine the stimulation time threshold, the shortest duration of cold exposure that causes a positive test reaction. Ice cube stimulation time thresholds of less than 3 min are associated with higher disease activity.

The patient in whom you suspect Symptomatic Dermographism. Dermographism or "writing on the skin" is the most common physical urticaria. It is caused by stroking the skin with varying degrees of pressure. Symptomatic Dermographism is distinguished and is a clinically distinct form of dermographism where the patient has itching and/or burning of the skin in addition to the common wheals formed by stroking of the skin. Patients may be identified by a history of itch without visible rash that is followed by linear wheals, or by the description or photograph of linear wheals.

Provocation is done by stroking the skin with firm pressure. This is often done with a tongue blade or the top of a pen. A linear wheal without itch is indicative of simple dermographism. A pruritic palpable wheal along the stroke line within 10 min of provocation is considered positive for symptomatic dermographism. Commercially available dermographometers are available that can provide a more uniform and measurable method of testing.

The patient in whom you suspect Cholinergic Urticaria. Cholinergic urticaria can be provoked by exercise, passive warming, emotional stress, and spicy foods. The patient typically reports a papular whealing associated with rash with small short-lived wheals but a larger area of pronounced flare that lasts for 15 min to an hour. Passive heating such as hot baths is a common trigger for cholinergic urticaria. Provocation testing is done with moderate physical exercise. The use of warm clothing and/or a warm room may facilitate the test. The patient should exercise using a standardized protocol appropriate for the patients' age and overall health condition. The appearance of the typical rash during exercise or within 10 min of discontinuation of exercise is diagnostic.

The patient in whom you suspect Delayed Pressure Urticaria. The name Delayed Pressure Urticaria is an apt description of the condition itself. This should be considered in patients who have lesions and itching at sites of pressure, such as belts, bra straps, and tops of socks. These patients may also have a history of urticaria from riding a bicycle, wearing tight clothes, or leaning against things such as their arms out of an open car window.

The traditional test for delayed pressure urticaria is the sand bag test, where a heavy sand bag is attached to a strap and then hung from the forearm, shoulder, or thigh for 15 min. The site is then observed for the next 24 h for erythema or urticaria. This test is not standardized, and there have been recent attempts to make the test more reproducible using weighted rods.

The patient in whom you suspect Vibratory Urticaria. Patients occasionally describe pruritus and urticaria after exposure to vibratory sources, such as handheld sanders. Some patients complain of symptoms while driving a car. A vortex vibrator is a common device that can test for vibratory urticaria. The patient holds his/her volar forearm to a vortex vibrator for 10 min at 1000 RPM. The site is then observed for 10 min after testing.

The patient in whom you suspect Solar Urticaria. Patients with solar urticaria typically have a history of developing wheals or erythema in sun exposed areas within minutes of sun exposure. Up to 16% of patients describe urticaria that also affects skin covered by thin clothing. Patients may respond to different wave lengths of light, with the most common spectrum being visible light, but may include UV-A and/or UV-B.[47]

Management of chronic inducible urticaria

The first preventive step to manage physical urticaria is the identification and avoidance of the physical trigger. Symptomatic pharmacotherapy first-line therapy includes nonsedating antihistamines in conventional doses followed by an

increase of the dose up to 4 times if the response is not satisfactory, and/or alternative medications (omalizumab, cyclosporine) as an additional resource (Fig. S2 in supplementary archive).[48–54] Tolerance induction by means of progressive and controlled long-term exposure to the stimulus is possible for cold urticaria,[55] heat urticaria,[56] and solar urticaria[57] (Supplemental Table 1).

URTICARIA IN SPECIAL SITUATIONS: CHILDHOOD, PREGNANCIES, IMMUNODEFICIENCIES

Childhood

Acute urticaria (AU) is more frequent in children and is usually caused by viral infections such as those of the upper respiratory tract. Food allergens (from eggs, milk, soy, peanuts, and wheat can induce IgE-mediated urticaria in young children and in older children most common food allergens include fish, seafood, and nuts. Other causes are drug hypersensitivity to nonsteroidal anti-inflammatory drugs and antibiotics[58] as well as insect bites such as mosquito (Supplemental Table 2).[59] The diagnosis of allergy in children with acute urticaria is necessary to avoid mislabeling children as allergic.[60] The prevalence of CU in children is estimated in less than 1%, and no significant difference among females or males has been found.[61] According to Netchiporouk et al the most common type of CU in childhood is CSU present in 78% of patients while 22% represent physical urticaria.[62] In children, urticaria commonly presents as a one-time acute episode that may last days to weeks, while a small proportion of patients are reported to progress to a chronic form of urticaria.[63] The differential diagnosis includes anaphylaxis, viral infections and serum sickness-like reactions.[64] In the pediatric population no markers have been identified to distinguish the evolution of the urticaria.[65]

Identification of potential triggers, when possible, and their avoidance is the first step in the management of a patient with urticaria.[58] The diagnostic workup includes a complete blood cell count, erythrosedimentation rate or C reactive protein (CRP).[66] Autoimmunity of type IIb, present in up to 40% of children with CU, can be confirmed by means of the ASST or the basophil histamine release test.[67,68]

Regarding the pharmacologic management of CU in children second generation antihistamines are the initial treatment of choice. According to EAACI/EDF/WAO guidelines the dose of second-generation antihistamines should be increased up to 4 times if the standard dose is not effective, (Supplemental Table 3).

Cetirizine use in teenagers and adults may cause somnolence and decrease the desire to perform activities. Therefore, other second generation antihistamines at higher than normal doses (bilastine or desloratadine) are suggested. Future studies establishing the safety of high-dose second generation antihistamines in children are needed.[64]

Large scale studies measuring the optimal dose and duration of treatment with omalizumab in pediatric patients with CSU are still required to include them in guidelines. It has been reported that 150 mg and 300 mg of omalizumab applied once monthly for 6 months may control most cases of CSU.[68] In several studies, the effectiveness of cyclosporin has been demonstrated in children. Renal function impairment and blood level monitoring may be an obstacle for its use.[69] In patients with acute severe exacerbations oral corticosteroids can be utilized at a dose of 0.5–1 mg/kg for 5–7 days.[70]

Pregnancy

Urticaria may not be treated in all pregnant woman, as it is not considered a life-threatening disorder. However, it may still affect patient's quality of life. Second-generation antihistamines remain the treatment of choice due to their non-sedating effects.[71] Increasing the dose up to 4 times the recommended dosage, at two-week intervals, may be needed to achieve control.[6]

Short 3-day courses of oral corticosteroids may be needed in case of severe exacerbations. However, maintenance systemic steroids are not indicated as treatment of urticaria in pregnant patients.[6]

First-generation antihistamines are not recommended when breastfeeding due to excretion in breast milk, being second generation

antihistamines such as loratadine and cetirizine the safer options.[72]

Regarding omalizumab, no evidence of an increased risk of major congenital anomalies among pregnant women exposed to omalizumab compared with a disease-matched unexposed cohort.[73]

Immunodeficiencies

Primary immunodeficiency diseases (PIDs) represent a heterogeneous group of inherited disorders caused by mutations in genes encoding functional proteins of the immune cells. It has been suggested that six million people are living with a PID worldwide.[73] They present as symptoms of autoimmunity, autoinflammation, malignancy, and allergic disease.[74]

Skin disorders may be the presenting clinical manifestations of a PID. For example, severe CU is present in some patients with immunodeficiency and autoinflammatory syndromes, and these conditions are to be differentiated from other phenotypes of CU (Supplemental Table 4).[75] In consequence, immunodeficiency and autoinflammatory syndromes should be suspected in patients with recurrent bouts of urticaria lasting months to years. In patients with those diseases CU is generally associated with other symptoms of inflammation such as fever, arthritis, serositis, hepatosplenomegaly, and ocular and/or neurologic involvement. Infection or malignancy should also be excluded through appropriate investigations.[76]

De Wit et al conducted a systematic search in 5030 patients and a broad spectrum of skin disorders was identified in 30 different types of PIDs.[77–80] Urticaria may be present in patients with combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, immunodysregulation polyendocrinopathy, enteropathy X-linked syndrome, congenital defects of phagocyte number or function, autoinflammatory disorders, and complement deficiencies.[81] (Supplemental Table 4)

CONCLUDING REMARKS

The prevalence of chronic urticaria in the population has been estimated to be between 0.1% and 1.0%. Quality of life of affected patients may be severely compromised, and the costs of the disease for the health system can be substantial. In recent years there have been remarkable advances in the understanding of the pathophysiology of urticaria that have prompted investigators to explore new medications, especially biologics, for patients with severe refractory urticaria. Multiple cell types are involved in the production of symptoms, mainly mast cells, basophils, eosinophils, T and B lymphocytes, and epithelial and endothelial cells. It is proposed that dysregulation of intracellular signaling pathways and autoimmune phenomena play a major role in mast cell/basophil activation leading to inflammatory mediator release in the skin resulting in wheals and angioedema.

According to medical records, 58.5% (394 of 673) of patients were reported to have had CSU-associated angioedema, and 41.0% whereas no identifiable trigger factors for the symptoms are present in a large proportion of affected subjects (chronic spontaneous urticaria), although in some of them external factors, mainly physical, could be suspected and proven (chronic inducible urticaria). It is also pertinent to mention that some patients may show a combined pattern of spontaneous and inducible urticaria.[82]

Currently biomarkers for the prognosis of CU and therapeutic response to different therapies have been identified which are useful for routine management. Finally, we recommend to follow the guidelines, to utilize validated patient reported outcome (PRO) instruments and to indicate medications with proven efficacy and safety. In the near future, new biologics and small molecules that are currently under investigation will be incorporated for the treatment of severe and refractory CU.

Abbreviations

ACE: angiotensin converting enzyme, AE: angioedema, AE-QoL: angioedema quality of life, ASST: autologous serum skin test, AU: acute urticaria, C5a: complement C5a, C5aR: complement C5a receptor, CRP: C reactive protein, CRTh2: chemoattractant receptor-homologous molecule expressed on T helper type 2 cells, CIndU: chronic

inducible urticaria, CsA: cyclosporine A, CSU: chronic spontaneous urticaria, CU: chronic urticaria, CUPP: Chronic Urticaria Patient Perspective, CU-Q2oL: chronic urticaria quality of life, DAMPs: damage-associated molecular patterns, DLQI: dermatology quality index, DNA: desoxyribonucleic acid, EBM: evidence-based medicine, ECP: eosinophil cationic protein, FcεRI: high affinity IgE receptor I, GA2 LEN: Global Allergy and Asthma European Network., GRADE: Grading of Recommendations Assessment Development and Evaluation., EAACI: European Academy of Allergy and Clinical Immunology., EDF: European Dermatology Foundation, HR4: histamine receptor 4, HRQoL: health-related quality of life, IgE: immunoglobulin E, IgG: immunoglobulin G, IgM: immunoglobulin M, IL-1: interleukin-1, IL-2: interleukin-2, IL-2R: interleukin-2 receptor, IL-3: interleukin-3, IL-4: interleukin-4, IL-5: interleukin-5, IL-17: interleukin-17, IL-24: interleukin-24, IL-31: interleukin-31, IL-33: interleukin-33, IL-4Rα: Interleukin-4 receptor alpha chain, IU: inducible urticaria, MBP: major basic protein, MRGPRX2: Mas-related G protein-coupled receptor X2, NSAIDs: nonsteroidal anti-inflammatory drugs, NS AHs: nonsedating antihistamines, OMA: omalizumab, PAF: platelet activating factor, PAMPs: pathogen-associated molecular patterns, PAR: protease-activated receptors, PGD2: prostaglandin 2, PPP$: power parity dollars, PIDs: Primary immunodeficiency diseases., PROs: patient-reported outcome, SCF: stem cell factor, TNF-α: tumor necrosis factor alpha, TLR: toll-like receptor, TSLP-R: thymic stromal lymphopoietin receptor., U: urticaria, UAS-7: urticaria activity score-7, UV-A: ultraviolet light-A, UV-B: ultraviolet light-B, WAO: World Allergy Organization.

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Appendix ASupplementary data
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REFERENCES

1. Zuberbier T, Balke M, Worm M, et al. Epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol*. 2010;35:869–873.
2. Baiardini I, Giardini A, Pasquali M, et al. Quality of life and patient's satisfaction in chronic urticaria and respiratory allergy. *Allergy*. 2003;58:621–623.
3. Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol*. 2006;154:294–298.
4. Delong LK, Culler SD, Saini SS, et al. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol*. 2008;144:35–39.
5. Sánchez-Borges M, Asero R, Ansotegui IJ, et al. WAO Position Paper. Diagnosis and Treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J*. 2012;5:125–147.
6. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393–1414.
7. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270–1277.
8. Keller K, Altrichter S, Ardelean E, et al. Chronic urticaria. Prevalence, course, prognostic factors and impact. *Hautarzt*. 2010:750–757.

9. Shahzad M, Sánchez-Borges M. Chronic urticaria: comparisons of US, European and asian guidelines. *Curr Allergy Asthma Rep*. 2018;18:36.
10. Sánchez-Borges M, Ansotegui I, Montero Jimenez J, et al. Comparative efficacy of non-sedating antihistamine updosing in patients with chronic urticaria. *WAO J*. 2014;7:33.
11. Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *Br J Dermatol*. 1998;138:635–638.
12. Kaplan AP. Treatment of chronic spontaneous urticaria. *Allergy Asthma Immunol Res*. 2012;4:326–331.
13. Maurer M, Roseń K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924–935.
14. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137:1742–1750.
15. Gimenez Arnau AM, Valero Santiago A, Bartra Tomas J, et al. Therapeutic strategy according to differences in response to Omalizumab in patients with chronic spontaneous urticaria. *J Investig Allergol Clin Immunol*. 2019;29:338–348.
16. Sánchez-Borges M, González Díaz S, Ortega-Martell JA, et al. Current and potential biological drugs for the treatment of chronic urticaria. *Immunol Allergy Clin NA*. 2020;40:609–623.
17. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol*. 2000;143:365–372.
18. Vena G, Cassano N, Colombo D, et al. Cyclosporine in chronic idiopathic urticaria: a double-blind randomized placebo-controlled trial. *J Am Acad Dermatol*. 2006;55:705–709.
19. Kaplan AP. Chronic spontaneous urticaria: pathogenesis and treatment considerations. *Allergy Asthma Immunol Res*. 2017;9:477–482.
20. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy*. 2010;65:1478–1482.
21. Fine LM, Bernstein JA. Guideline of chronic urticaria beyond. *Allergy Asthma Immunol Res*. 2016;8:396–403.
22. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol Pract*. 2018;6:586–599.
23. Ohtsuka T. Response to oral cyclosporine therapy and high sensitivity-CRP level in chronic idiopathic urticaria. *Int J Dermatol*. 2010;49:579–584.
24. Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. *Pediatr Dermatol*. 2009;26:409–413.
25. Savic S, Marsland A, Mc Kay D, et al. Retrospective case note review of CSU outcomes and adverse effects in patients treated with omalizumab or cyclosporine in UK secondary care. *All Asthma Clin Immun*. 2015;11:21.
26. Marchese ML, Eimer L, Stringa O. Cyclosporin and its use in dermatology: Introduction. *Arch Argent Dermatol*. 2014;64:89–97.
27. Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F, Gonzalez-Aveledo LA. Biomarkers of treatment efficacy in patients with chronic spontaneous urticaria. *Eur Ann Allergy Clin Immunol*. 2018;50:5–9.
28. Iqbal K, Bhargava K, Skov PS, et al. A positive serum basophil histamine release assay is a marker for cyclosporine-responsiveness in patients with chronic spontaneous urticaria. *Clin Transl Allergy*. 2012;2:19.
29. Hollander SM, Joo SS, Wedner HJ. Factors that predict the success of cyclosporine treatment for chronic urticaria. *Ann Allergy Asthma Immunol*. 2011;107:523–528.
30. Asero R. Plasma D-diner levels and clinical response to cyclosporine in severe chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2015;135:1402–1403.
31. Baek YS, Jeon J, Kim JH, Oh CH. Severity of acute and chronic urticaria correlates with D-dimer level, but not C-reactive protein or total IgE. *Clin Exp Dermatol*. 2014;39:795–800.
32. Kulthanan K, Subchookul C, Hunnangkul S, et al. Factors predicting the response to cyclosporine treatment in patients with chronic spontaneous urticaria: a systematic review. *Allergy Asthma Immunol Rev*. 2019;11:736–755.
33. Bansgaard N, Skov L, Zachariae C. Treatment of refractory chronic spontaneous urticaria with adalimumab. *Acta Derm Venereol*. 2017;97:524–525.
34. Wilson LH, Eliason MJ, Leiferman KM, et al. Treatment of refractory chronic urticaria with tumor necrosis alfa inhibitors. *J Am Acad Dermatol*. 2011;64:1221–1222.
35. Arkwright PU. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. *J Allergy Clin Immunol*. 2009;123:510–511.
36. Chakrawarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. *J Allergy Clin Immunol*. 2011;128:1354–1355.
37. Steinweg SA, Gaspari AA. Rituximab for the treatment of recalcitrant chronic autoimmune urticaria. *J Drugs Dermatol JDD*. 2015;14:1387.
38. Mallipedi R, Grattan CE. Lack of response of severe steroid-dependent chronic urticaria to Rituximab. *Clin Exp Dermatol*. 2007;32:333–334.
39. Ghazan-Shahi S, Ellis AK. Severe steroid-dependent idiopathic angioedema with response to Rituximab. *Ann Allergy Asthma Immunol*. 2011;107:374–376.
40. Maurer M, Gimenez Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med*. 2019;381:1321–1332.
41. Altrichter S, Staubach P, Pasha M, et al. Clinical activity of AK002, an Anti-SIGLEC-8 antibody in multiple forms of uncontrolled chronic urticaria. *Ann Allergy Asthma Immunol*. 2019;123:S27–S28.
42. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticarial. *Allergy Clin Immunol Pract*. 2019;7:1659–1661.
43. Neel A, Henry B, Barbarot S, et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: a French multicenter study. *Autoimmun Rev*. 2014;13:1035–1041.
44. De Koning HG, Schalkjuik J, Meer Van Der, Simon A. Successful canakinumab treatment identifies IL-1β as a pivotal mediator in Schnitzler syndrome. *J Allergy Clin Immunol*. 2011;128:1352–1354.

45. Krause K, Tsianakas A, Wagner N, et al. Efficacy and safety of canakinumab in Schnitzler syndrome: a multicenter randomized placebo-controlled study. *J Allergy Clin Immunol*. 2017;139:1311–1320.

46. Lachman HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med*. 2009;360:2416–2425.

47. Krause K, Mahamed A, Weller K, et al. Efficacy and safety of canakinumab in urticarial vasculitis: an open-label study. *J Allergy Clin Immunol*. 2013;132:751–754.

48. Pérez-Ferriols A, Barnadas M, Gardeazábal J, et al. Solar urticaria: epidemiology and clinical phenotypes in a Spanish series of 224 patients. *Actas Dermosifiliogr*. 2017 Mar;108:132–139.

49. Maurer M, Fluhr J, Khan DA. How to approach chronic inducible urticaria. *J Allergy Clin Immunol Pract*. 2018;6:1119–1130.

50. Sánchez-Borges M, González-Aveledo L, Caballero-Fonseca F, Capriles-Hulett A. Review of physical urticarias and testing methods. *Curr Allergy Asthma Rep*. 2017;17:51.

51. Dressler C, Werner RN, Eisert L, et al. Chronic inducible Urticaria: a systematic review of treatment options. *J Allergy Clin Immunol*. 2018;141:1726–1734.

52. Kocaturk E, Kuteyla Can P, Adbas PE, et al. Management of chronic inducible uriticaria according to the guidelines: a prospective controlled study. *J Dermatol Sci*. 2017;87:60–69.

53. Zuberbier T, Aberer W, Asero R, et al. EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64:1427–1443.

54. Kolkhir P, Pogorelov D, Darlenski R, et al. Management of chronic spontaneous urticaria: a worldwide perspective. *World Allergy Org J*. 2018;11:14.

55. Maurer M, Altrichter S, Schmetzer O, et al. Immunoglobulin E-mediated autoimmunity. *Front Immunol*. 2018;9:689.

56. Black AK, Sibbald RG, Greaves MW. Cold urticaria treated by induction of tolerance. *Lancet*. 1979;2:964.

57. Leigh IM, Ramsay CA. Localized heat urticaria treated by inducing tolerance to heat. *Br J Dermatol*. 1975;92:191–194.

58. Ramsay CA. Solar urticaria treatment by inducing tolerance to artificial radiation and natural light. *Arch Dermatol*. 1977;113:1222–1225.

59. Marrouche N, Grattan C. Childhood urticaria. *Curr Opin Allergy Clin Immunol*. 2012;12:485–490.

60. Sanchez-Borges M, Capriles-Hulett A, Caballero- Fonseca F, Gonzalez-Aveledo L. Urticaria en niños atendidos en servicios de Alergología. *Rev Alerg Mex*. 2014;61:90–98.

61. Ben-Shoshan M, Grattan CE. Management of pediatric urticaria with review of the literature on chronic spontaneous urticaria in children. *J Allergy Clin Immunol Pract*. 2018;6:1152–1161.

62. Caffarelli C, Paravati F, El Hachem M, et al. Management of chronic urticaria in children: a clinical guideline. *Ital J Pediatr*. 2019;45:101.

63. Netchiporouk E, Sasseville D, Moreau L, et al. Evaluating comorbidities, natural history, and predictors of early resolution in a cohort of children with chronic urticaria. *JAMA Dermatol*. 2017;153:1236–1242.

64. Balp MM, Weller K, Carboni V, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2018;29:630–636.

65. Magen E, Zueva E, Mishal J, Schlesinger M. The clinical and laboratory characteristics of acute spontaneous urticaria and its progression to chronic spontaneous urticaria. *Allergy Asthma Proc*. 2016;37:394–399.

66. Schaefer P. Urticaria: evaluation and treatment. *Am Fam Physician*. 2011;83:1078–1084.

67. Grattan C. Autoimmune chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2018;141:1165–1166.

68. Netchiporouk E, Moreau L, Rahme E, et al. Positive CD63 basophil activation tests are common in children with chronic spontaneous urticaria and linked to high disease activity. *Int Arch Allergy Immunol*. 2016;171:81–88.

69. Asero R, Casalone R, Iemoli E. Extraordinary response to omalizumab in a child with severe chronic urticaria. *Eur Ann Allergy Clin Immunol*. 2014;46:41–42.

70. Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. *J Allergy Clin Immunol Pract*. 2014;2:434–438.

71. Larenas-Linnemann D, Medina-Avalos M, Ortega-Martell JA, et al. Guía Mexicana para el Diagnóstico y el Tratamiento de la Urticaria. *Rev Alerg Mex*. 2014;61(Supl. 2):S117–S193.

72. Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. *J Pharmacol Pharmacother*. 2012;3:105.

73. Namazy JA, Blais L, Andrews EB, et al. Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. *J Allergy Clin Immunol*. 2020 Feb;145(2):528–536.

74. Lawlor F. Urticaria and angioedema in pregnancy and lactation. *Immunol Allergy Clin*. 2014;34:149–156.

75. Bousfiha AA, Jeddane L, Ailal F, et al. Primary immunodeficiency dis- eases worldwide: more common than generally thought. *J Clin Immunol*. 2013;33:1–7.

76. de Vries E. European Society for Immunodeficiencies. Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. *Clin Exp Immunol*. 2012;167:108–119.

77. Sillevis Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. *Curr Opin Pediatr*. 2013;25:492–497.

78. Youssef MJ, Chiu YE. Eczema and urticaria as manifestations of undiagnosed and rare diseases. *Pediatr Clin*. 2017;64:39–56.

79. Sinikumpu SP, Huilaja L, Jokelainen J, et al. High prevalence of skin diseases and need for treatment in a middle-aged population. A Northern Finland Birth Cohort 1966 study. *PLoS One*. 2014;9:e99533.

80. Bilgili ME, Yildiz H, Sarici G. Prevalence of skin diseases in a derma- tology outpatient clinic in Turkey. A cross-sectional, retrospective study. *J Dermatol Case Rep*. 2013;7:108–112.

81. Furue M, Yamazaki S, Jimbow K, et al. Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study. *J Dermatol*. 2011;38:310–320.

82. Maurer M, Abuzakouk M, Berard F, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy*. 2017;72:2005–2016.

83. De Wit J, Brada RJK, van Veldhuizen J, et al. Skin disorders are prominent freatures in primary immunodeficiency diseases: a systematic overview of current data. *Allergy*. 2019;74:464–482.

84. Gernez Y, Freeman AF, Holland SM, et al. Autosomal dominant hyper-IgE syndrome in the USIDNET registry. *J Allergy Clin Immunol Pract*. 2018;6:996–1001.

85. Moin A, Farhoudi A, Moin M, et al. Cutaneous manifestations of primary immunodeficiency diseases in children. *Iran J Allergy, Asthma Immunol*. 2006;5:121–126.

86. Aghamohammadi A, Cheraghi T, Gharagozlou M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. *J Clin Immunol*. 2009;29:130–136.

87. Patrizi A, Ricci G, Cassoli C, et al. Dermatologic diseases associated with IgA deficiency. *G Ital Dermatol Venereol*. 1992;127:325–329.

88. Magen E, Masalha A, Waitman DA, et al. Prevalence of dermatologic diseases among patients with selective immunoglobulin A deficiency. *Allergy Asthma Proc*. 2017;38: 70–77.

89. Ferre EM, Rose SR, Rosenzweig SD, et al. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. *JCI Insight*. 2016;1:e88782.

90. Zaidi G, Bhatia V, Sahoo SK, et al. Autoimmune polyendocrine syndrome type 1 in an Indian cohort: a longitudinal study. *Endocr Connect*. 2017;6:289–296.

91. Sahin S, Adrovic A, Barut K, et al. Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. *Rheumatol Int*. 2018;38:129–136.

92. Wu J, Wang WF, Zhang YD, Chen TX. Clinical features and genetic analysis of 48 patients with chronic granulomatous disease in a single center study from Shanghai, China (2005-2015): new studies and a literature review. *J Immunol Res*.. 2017:8745254.

93. Aderibigbe OM, Priel DL, Lee CC, et al. Distinct cutaneous manifes- tations and cold-induced leukocyte activation associated with PLCG2 mutations. *JAMA Dermatol*. 2015;151: 627–634.

94. El-Darouti MA, Marzouk SA, Abdel-Halim MR. Muckle-Wells syn- drome: report of six cases with hyperpigmented sclerodermoid skin lesions. *Int J Dermatol*. 2006;45:239–244.

95. Mehr S, Allen R, Boros C, et al. Cryopyrin-associated periodic syn- drome in Australian children and adults: epidemiological, clinical and treatment characteristics. *J Paediatr Child Health*. 2016;52:889–895.