

The Maddening Itch: An Approach to Chronic Urticaria

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■ Abstract

Chronic spontaneous urticaria (CSU) is defined as the presence of urticaria with daily or almost daily symptoms for 6 weeks or more. CSU affects 0.1%-0.8% of the population. Its pathogenesis involves autoimmunity, abnormalities in signal transduction, and the action of histamine on H₁ receptors.

Investigation of CSU should be guided by a thorough history and physical examination. A concise laboratory evaluation, including the CU index, is recommended. This index can provide useful data on severity and response to therapy.

Initial treatment should involve increasing doses of nonsedating antihistamines until the intended effect is achieved. Only when a patient is unresponsive to high-dose nonsedating antihistamines (or sedating antihistamines) can we consider CSU refractory and consider immunomodulatory therapy. The most promising drugs are cyclosporine and, more recently, omalizumab.

Key words: Spontaneous chronic urticaria. CU index. FcεRI. Omalizumab.

■ Resumen

La urticaria crónica espontánea (CSU) se define como la presencia de urticaria durante al menos 6 semanas, con síntomas diarios o prácticamente diarios que afecta al 0,8-1% de la población. Su patogénesis puede deberse tanto a la unión de la histamina a sus receptores H₁, como a autoinmunidad o a alteraciones en las señales de transducción.

El diagnóstico de la urticaria crónica (CU) se centra en la historia clínica y en el examen físico. Es aconsejable la realización de una analítica sucinta así como la realización de un test de CU que orienta la severidad clínica y la respuesta al tratamiento.

El tratamiento debe iniciarse con dosis progresivas de antihistamínicos no sedantes (nsAH) hasta conseguir un control adecuado. Sólo puede etiquetarse como CSU refractaria cuando el paciente no responde a altas dosis de antihistamínicos (AH) sedantes o no sedantes y entonces plantearse un tratamiento inmunomodulador. La ciclosporina es uno de los mejores tratamientos de este grupo y más recientemente el omalizumab.

Palabras clave: Urticaria crónica espontánea. Índice CU. FcεRI. Omalizumab.

Urticaria is defined as pruritic wheals that develop rapidly, with central swelling of varying sizes surrounded by erythema. The duration of individual lesions ranges from 1 to 24 hours. Urticaria may be accompanied by angioedema, which is defined as cutaneous or mucosal swelling that is generally nonpruritic and lasts 1-3 days [1]. Acute urticaria, which lasts less than 6 weeks, is often allergic (eg, food or drugs). Chronic spontaneous urticaria (CSU) is defined as daily or almost daily wheals for more than 6 weeks and is synonymous with chronic idiopathic urticaria (CIU) [2]. It affects 0.1% [3] to 0.8% of the population [4], including a subpopulation with positive autoimmune serology (45%) to the IgE receptor, IgE, and antithyroid antibodies (ATA) [5]. The incidence of low-titer positive antinuclear antibody (ANA) is also increased [6]. Persistence and severity of

symptoms correlates with positive autoimmune serology [7], more intense inflammation in skin biopsy, and resistance to antihistamines [8,9]. A third general category of urticaria comprises physical urticaria, such as cold urticaria, cholinergic urticaria, and dermatographism, none of which will be addressed here.

Vasoactive mediators released from dermal mast cells play a key role in the pathogenesis of CSU. Despite the presence of other mediators (eicosanoids, cytokines, and proteases), histamine is the most prominent and acts on H₁ receptors (85%) and H₂ receptors (15%) in the skin. While histamine binding to H₁ receptors leads to pruritus (by stimulation of C fibers), binding to receptors on postcapillary venules induces vasodilation, increased vascular permeability, and edema (mediated in part through nitric oxide) [5].

Mechanisms other than histamine release have been implicated in CSU/CIU and include autoimmunity (eg, ATA) and abnormalities in basophil signal transduction [2].

IgG autoantibody against IgE (5-10%) or its high affinity receptor FcεRI (30-40%) is produced in 50% of patients with CSU/CIU. The cross-linking autoantibody against the α subunit of FcεRI induces degranulation of cutaneous mast cells and blood basophils, which is followed by release of histamine [10]. IgG1 and IgG3 are the main anti-FcεRI autoantibody subclasses found in CSU [5]. The role of complement was further confirmed when it was demonstrated that in vitro release of histamine from normal human basophils and mast cells by anti-FcεRI autoantibodies is augmented by C5a [10,12,13].

The findings that favor an autoimmune etiology in CSU/CIU are as follows: (1) Autologous intradermal injection of sera from some patients with CSU causes a wheal and flare reaction [14]; (2) Histology of urticarial lesions reveals eosinophils, mast cells, and activated CD4+ T cells [15]; (3) IgG autoantibodies to the α subunit of FcεRI or to IgE itself have been demonstrated in the serum of CU patients [15]; (4) A reduced percentage of blood basophils (perhaps recruited to the skin) is found in patients with CSU and histamine-releasing autoantibodies [15]; (5) HLA-DR alleles that are generally associated with autoimmune disease are increasingly frequent [2].

The association between thyroid autoimmunity and CSU/CIU has long been observed [16]. Leznoff et al [16] and Leznoff and Sussman [17] reported a higher incidence of thyroglobulin and/or thyroid peroxidase antibodies in CSU patients than in the general population (15%-30% vs 3%-6%, respectively) [16,17]. Nevertheless, many authors consider this an autoimmune association that is not necessarily pathogenic and, therefore, do not favor thyroid supplementation in patients without overt hypothyroidism [16].

Cross-linking of FcεRI on the surface of mast cells and basophils leads to the release of mediators through phosphorylation of tyrosines in immunoreceptor tyrosine-based activation motifs (ITAMs) associated with membrane receptors, activation and binding of spleen tyrosine kinase (Syk) to ITAMs, and subsequent phospholipase C activation and increase in intracellular calcium. This process culminates in the activation of a series of events that lead to upregulation of the transcription factors responsible for production of leukotrienes and cytokines, degranulation, and release of mediators and eicosanoids through activation of phospholipase A2 [18].

Saini et al [19] reported more intense release of histamine in cultured mast cells from CSU patients than from controls. The phosphoinositide lipid phosphatases SHIP1 (Src homology 2 domain-containing inositol phosphatase 1) and SHIP2 downregulated mast cell and basophil activation and degranulation, whereas Syk promoted them.

Vonakis et al [20] reported hyporesponsiveness of blood basophils in 50% of patients with CSU due to excessive SHIP activity that dephosphorylates kinases (namely Syk) and leads to decreased cell response. This hyporesponsiveness was reversed once the symptoms improved, suggesting an association with the pathogenesis of urticaria, but perhaps also serving as a biomarker of responsiveness.

Investigation of CSU should be guided by a thorough history in order to ensure a correct diagnosis. Lesions should

be characterized in terms of wheal dimensions, presence of angioedema, duration, association with physical stimuli, disease chronology, remissions, and response to therapy. It is essential to exclude potential allergic, contact, infectious, pharmacologic, or systemic etiologies. Patients presenting with CSU/CIU have no evident allergologic or infectious etiology. The laboratory evaluation can include a differential blood count, erythrocyte sedimentation rate, chronic urticaria (CU) index (anti-IgE receptor and/or anti-IgE), and thyroid workup including thyroid-stimulating hormone, free thyroxine 4, and ATA (both antithyroglobulin and antithyropoxidase antibodies).

Various tests can be used to evaluate autoimmunity, although the CSU index is currently considered the gold standard for identification of the subpopulation with chronic autoimmune urticaria [2].

The autologous serum skin test (ASST) reflects the presence of histamine-releasing autoantibodies in most instances, but is less specific (ie, other factors may yield a positive result [7,18]) and less sensitive.

The commercial basophil histamine release assay screens for a functional autoantibody to FcεRIα (eg, CU index) (35-40%) or to IgE (5%). Platzer et al [21] found that it had a specificity and sensitivity of 75% [21]. The CU index provides a qualitative measure of autoimmunity and shows a rough quantitative correlation with disease severity [2,22,23]. Biagtan et al [23] calculated the sensitivity and specificity of a CU index ≥10% to be 51% and 81%, respectively. A positive index favored an autoimmune basis for CSU and was correlated with increased severity and refractoriness to therapy [23], thus providing a rationale for more aggressive immunosuppressive therapy [24]. The condition of this subpopulation, although more severe, appears more responsive to treatment with cyclosporine [25,26].

With regard to thyroid function and ATA, a positive association has been reported between CSU and Hashimoto thyroiditis and Graves disease (the latter to a lesser extent) [16,27]. Although 27% of CSU patients present with ATA and 19% are noneuthyroid, there is little evidence that treating the underlying condition will alter the course of urticaria [18].

Viswasathan et al [6] examined the association between autoimmune biomarkers in CSU and disease severity by evaluating ANA, ATA (antithyroglobulin and antithyropoxidase antibodies), and the CU index. The authors compared the odds ratios (OR) of a refractory outcome for different autoimmune biomarkers in CIU and found that the CU index had the strongest independent correlation with disease severity (Table).

Table 1. Odds Ratio of Different Autoimmune Biomarkers of a Refractory Outcome in CSU

Biomarkers	OR	P	Cost, US\$/€
CU index	4.5	.005	436/337
ANA + ATG + ATPO	3.1	.01	330/255
ANA	2.3	.04	84/65

Abbreviations: ANA, antinuclear antibody; ATG, antithyroglobulin antibody; ATPO, anti-thyroid peroxidase antibody; CU, chronic urticaria; OR, odds ratio. ^aAdapted from Viswanathan et al [6].

Practical measures to consider for the treatment of chronic urticaria include avoidance/minimization of aggravating factors, such as drugs (nonsteroidal anti-inflammatory drugs and aspirin), alcohol, minor viral infections, stress, and local heat and friction [15,18,28].

The EAACI/GA2LEN/EDF guidelines for treatment of CU [1] recommend a stepwise approach: (1) nonsedating antihistamine (up to 4-fold); (2) change to a different nonsedating antihistamine or addition of a leukotriene antagonist (if symptoms persist); (3) cyclosporine A, dapsone, or omalizumab (if symptoms persist); (4) systemic corticosteroids (3 to 7 days) for treatment of exacerbations.

The first line of treatment consists of histamine H₁-receptor antagonists [29], since most symptoms of CU are mediated by H₁ receptors located on sensory nerves and endothelium [15]. Antihistamines are inverse agonists that bind to the H₁ receptor and induce an inactive conformation that competes with histamine to induce an active conformation. Additional effects include the following: inhibition of secretion of eicosanoids, leukotrienes, and cytokines; inhibition of eosinophil migration; and downregulation of VCAM-1 mRNA activation and expression in endothelial cells, owing to inhibition of NF- κ B induction [15]. According to the EAACI/GA2LEN/EDF guideline, therapy should be started with second-generation antihistamines, which have fewer adverse effects of first-generation antihistamines (sedation, drowsiness, and mucosal dryness) [1].

Second-generation antihistamines are effective in mild urticaria, yet in more severe cases the dose must be increased [29,30] (the effect of antihistamines in urticaria is dose-dependent [31]). If ineffective, an alternative second-generation antihistamine [5] or a first-generation antihistamine can be tried [29]. According to Kaplan [32], nonresponse to first-generation antihistamines (hydroxyzine or diphenhydramine) at doses of up to 50 mg qid confirmed that patients were considered refractory to therapy, thus effectively limiting the frequency of corticosteroid use before cyclosporine or omalizumab became viable alternatives. This dose is actually equivalent to 6 cetirizine pills (60 mg) per day [33,34]. The efficacy and safety of dose increases have been assessed by Staevska et al [35] and Siebenhaar et al [36].

If high-dose antihistamines fail to control CSU, other currently available well-documented options include corticosteroids, cyclosporine, and omalizumab. Although the EAACI/GA2LEN/EDF guideline [1] mentions leukotriene antagonists and H₂ receptor antagonists as add-on therapy, firm evidence of efficacy is lacking [37]. An update of the guideline (in press) eliminates H₂ receptor antagonists as an alternative.

Corticosteroids are recommended by EAACI/GA2LEN/EDF guidelines for the treatment of exacerbations [1]. However, long-term studies of their effect and optimal dosage are lacking. The proposed mechanism for corticosteroid action involves nuclear inhibition of gene expression and coding of messenger RNA, thus promoting synthesis of proinflammatory interleukins and cytokines that could suppress cutaneous effects [38]. Corticosteroid therapy is highly efficacious [29,39], yet limited by its multiple dose-dependent and time-dependent side effects (diabetes, hypertension, osteoporosis, and gastrointestinal bleeding). The EAACI/GA2LEN/EDF guideline proposes a short course (3-7 days)

in CU exacerbations in order to reduce disease duration [1]. Nonetheless, repeated short tapering bursts of corticosteroids can be more problematic than a fixed dose on alternate days with a slower taper and simultaneous maximum dose of antihistamines. The optimal approach involves starting prednisone at 20 mg every other day and decreasing by 2.5-5 mg every 3 weeks down to 10 mg, at which point 2.5-5 mg is administered every other day. Another strategy involves daily prednisone at 10-12 mg/d with a taper of 1 mg every 7-10 days [38].

Cyclosporine has a better risk-benefit ratio than corticosteroids [1]. It is an immunosuppressive and anti-inflammatory drug that downregulates type 1 helper T cells and T-cell dependent antibody formation and inhibits anti-IgE stimulated histamine release from basophils and mast cells [18]. A history of urticaria, shorter duration of hives, and a positive CU index have been confirmed as predictors of therapy with this agent [25].

Several authors show low-dose cyclosporine to be effective in remission of/improvement in symptoms [25,40,41]. The incidence of the main side effects (nephrotoxicity and hypertension) gives cause for concern [15]. Therefore, initial and subsequent assessment (every 6 weeks) of blood pressure, serum urea nitrogen, and creatinine is recommended, as is urinalysis [42]. A typical dose is 3-3.5 mg/kg/d, which is less than the dose typically used for immunosuppression in transplantation.

The recombinant monoclonal antibody omalizumab is approved for treatment of moderate to severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids and long-acting β -agonists, although it has not yet been approved in Europe for urticaria. It has been used off-label and in research studies for the treatment of severe CSU. Omalizumab blocks binding of IgE to Fc ϵ RI on the surface of target cells (mast cells and basophils), leading to a decrease in receptor expression and release of inflammatory mediators. It is absorbed slowly, with peak concentrations after a mean of 7-8 days and a mean terminal half-life of 19-22 days [43].

The efficacy and tolerance of omalizumab in patients with CU were first demonstrated in a single-blind, placebo-controlled trial (phase I) where 12 patients with chronic antihistamine-resistant autoimmune urticaria were treated for 4 weeks with placebo followed by omalizumab for 16 weeks. A response was observed in 11 patients: symptoms resolved completely in 7 and a significant improvement was recorded in 4 [44]. Similar results were observed in 2 placebo-controlled trials and in various case reports, some of which included physical urticaria [45].

Saini et al [43] reported a randomized, double-blind, placebo-controlled study with patients taking 75, 300, and 600 mg of omalizumab in addition to a stable dose of H₁ receptor antagonist for 4 weeks and concluded that single-dose omalizumab (300 or 600 mg) provided rapid and effective therapy of CSU in patients who remained symptomatic despite therapy with H₁ receptor antagonists. The optimal dose of omalizumab was 300 mg [43]. Maurer et al [46] evaluated CU patients with IgE against thyroperoxidase and found that omalizumab (75-375 mg) resulted in a rapid and significant reduction in urticaria scores and protection from development of wheals in 70.4% [46].

In both trials, omalizumab was highly effective, safe, and well tolerated. To date, individual response rates have varied, but the overall response reveals significant clinical improvement, which, in some patients [46], occurs within a few days of the first dose being administered. Downregulation of the IgE receptor begins after some weeks; however, its mechanism of action is unclear.

A recently published phase 3 study by Maurer et al [47] demonstrated efficacy at monthly doses of 150 mg or 300 mg over a 12-week study period, with low toxicity and striking responses for pruritus and wheal formation, suggesting that it might be the most efficacious choice in patients whose disease is refractory to antihistamines [47]. This was confirmed and extended to include patients who were unresponsive to H₁ antihistamines, H₂ receptor antagonists, and leukotriene antagonists [48].

Despite affecting less than 1% of the population, CSU is associated with decreased quality of life, constant pruritus, disfigurement, and high morbidity owing to its chronic course and the likelihood of relapses. It is critical to understand the pathophysiology of CSU in order to make a reasonable patient evaluation and ensure a therapeutic approach that begins by progressively increasing the dose of antihistamines before advancing to more potent anti-inflammatory or immunosuppressive therapies.

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Conflicts of Interest

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