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Chronic Spontaneous Urticaria: The Devil's itch

Sarbjit S. Saini, M.D.¹ and Allen P. Kaplan, M.D.²

¹Department of Medicine, Division of Allergy and Clinical Immunology, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Room 2B.71B, Baltimore, MD 21224

²Department of Medicine, Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, Charleston, SC

Abstract

Chronic urticaria is defined as the presence of urticaria for a period exceeding 6 weeks, assuming symptoms for most days of the week. It is divided into chronic inducible urticarias (CIndU) and chronic spontaneous urticaria (CSU), previously termed chronic idiopathic urticaria (CIU). The latter designation emphasizes that patients can experience urticaria independent of any exogenous stimulus even if one can define circumstances that may worsen symptoms. A search for such an external “cause” is fruitless, since the underlying abnormality is “intrinsic”, whether it is autoimmune, or some unknown process. Approximately 40% of patients with CSU report accompanying episodes of angioedema, whereas 10% have angioedema as their primary manifestation. In most cases, it is a self-limiting disorder, persisting for 2–5 years in the majority of cases, although 20% of patients suffer for more than 5 years. The treatment that has evolved is largely empiric, based on double-blind, placebo-controlled studies whenever possible, but is not yet targeted to any particular pathogenic mechanism. In this article, we review the current status regarding pathogenesis, discuss the diagnostic workup, and update the approach to treatment including consideration of published guidelines, our own experience, and guideline updates that are being prepared.

Keywords

Chronic Urticaria; Treatment; Pathogenesis

Introduction

Chronic urticaria is defined as the presence of urticaria for a period exceeding 6 weeks, assuming the presence of symptoms for most days of the week. It is divided into chronic inducible urticarias (CIndU, also called physical urticarias) and chronic spontaneous

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urticaria (CSU), previously termed chronic idiopathic urticaria (CIU) ^{1, 2}. Chronic inducible urticarias are identified based on the history of a consistent stimulus that initiates lesions, which are typically short-lived and fleeting, lasting a few minutes up to 2 hours. When biopsied, there is no cellular infiltrate. In contrast, the term CSU emphasizes that patients can experience urticaria independent of any exogenous stimulus even if one can define circumstances that may worsen symptoms. Thus, a search for such an external “cause” in CSU is a fruitless effort since the underlying abnormality is “intrinsic”. Approximately 40% of patients with CSU will report accompanying episodes of angioedema or deeper swelling of dermal or mucosal tissues, whereas 10% have angioedema as their primary manifestation^{3, 4}. In most cases, it is a self-limiting disorder, persisting for 2–5 years in the majority of cases, although 20% of patients suffer for more than 5 years ^{5–7}.

The treatment for CSU that has evolved is based on double-blind, placebo-controlled studies whenever possible, but is not yet targeted to any particular pathogenic mechanism. While the efficacy of omalizumab in disease has implicated IgE and IgE receptors in disease pathogenesis, a clear biomarker that segregates responders from non-responders remains elusive. In this article, we will review the current status regarding pathogenesis, discuss what are the essentials of a diagnostic workup, and update the approach to treatment including consideration of published guidelines, our own experience, and guideline updates that are being prepared.

Pathogenesis

Wheals and angioedema in CSU appear to involve the degranulation of skin mast cells, which release histamine, proteases and cytokines with generation of platelet-activating factor and other arachidonic acid metabolites (prostaglandin D₂, leukotrienes C₄, D₄ and E₄). These mediators induce vasodilatation, increase vascular permeability, and stimulate sensory nerve endings that lead to swelling, redness and itch⁸. A lesion site or wheal is characterized by edema, mast cell degranulation, and a perivascular infiltrate of cells- CD4⁺ lymphocytes, monocytes, neutrophils, eosinophils and basophils and has similarities to the infiltrate seen in the allergen late phase reaction ^{9–12}. The lesion cytokine profile shows T cell expression of IL-4, IL-5, and gamma interferon suggesting a mixed Th1/Th2 response ¹⁰. More recently, epithelial derived cytokines that favor Th2 profile including IL-33, IL-25, and TSLP are detected in the dermis of lesional skin along with the vasoactive agents VEGF and CGRP, but these factors were not observed in uninvolved skin ^{13, 14}. Although several theories exist regarding the pathogenesis of chronic urticaria, none have been conclusively established¹⁵. Many studies have examined the autoimmune theory of disease and also the validity of serologic tests to establish an autoimmune basis. Additional theories include abnormalities of tissue mast cells and basophils as well as other serologic factors.

Mast cells

A role for mast cells is supported by tissue biopsy evidence of mast cell degranulation, elevated histamine content⁸ measured from over CSU skin lesions, and the clinical response to anti-histamines ¹⁶. Whether skin mast cells in CSU are increased or not remains controversial. Some studies reported an increase^{11, 17, 18} while other studies reported

numbers similar to levels in healthy skin.^{9, 19} In addition, indirect measures of mast cell presence such as total serum tryptase are within the normal range but higher than the average measured in atopic and non-atopic controls. However, CSU patients who report extracutaneous systemic symptoms have a higher average tryptase than those with skin-limited symptoms²⁰. Mast cells express multiple receptors that are susceptible to activation (e.g., chemokine, prostaglandin, Toll-like, or immunoglobulin receptors).^{15, 21} The exact mechanism for mast cell activation in CSU is still not clear, but several theories are discussed below.

Various autoimmune diseases are more prevalent in subjects with CSU^{22, 23}. Based on the recognition of increased thyroid disease expression in CSU, the concept of underlying autoimmunity as the cause of disease emerged in the 1980s along with a potential role for IgG class autoantibodies. Specifically, it is thought that autoantibodies to IgE or IgE receptors exist in 30–40 % of individuals, leaving 60% without a proposed pathogenic mechanism²⁴. Of note, a recent study has provided the first evidence for the presence of autoreactive CD4+T cells to the IgE receptor alpha chain in a subset of CSU subjects, and that most of these autoreactive T cells secrete IFN γ .²⁵ In a recent database survey of 13,000 patients relative to 10,000 control subjects the following diseases were noted to be increased among CU patients: thyroid disorders, celiac disease, Sjogren syndrome, SLE, rheumatoid arthritis, and type I diabetes.²⁶ This IgG autoantibody theory and its controversial clinical significance, and association of CSU with autoimmune diseases has been the topic of a recent reviews and will not be covered in depth here^{15, 27–29}.

Another theory is that enhanced skin mast cell releasability occurs in active CSU. For example, compound 48/80-induced histamine responses via skin chambers have been shown to be increased in patients with CSU as compared with healthy controls and this enhanced releasability resolves with CSU remission^{19, 30}. Recently, levels of Mas-related gene X2 (MrgX2), a novel G protein coupled receptor (GPCR) expressed on human mast cells that binds basic proteins including compound 48/80, are known to be increased in the skin of patients with CSU.^{31,32} It has also been noted that CD34+-derived mast cells of subjects with CSU spontaneously release histamine upon sensitization by IgE³³. However, the cause of this heightened release state of mast cells remains elusive.

Several studies have shown that the blood coagulation cascade is active in CSU and may mirror disease activity (see below). Recent work by Yanase et al has proposed a new pathway for tissue mast cell activation. Recognizing the evidence for coagulation system activation, they demonstrated that intravascular histamine release along with an infection stimulus producing TLR activation (via TLR 3, 4, 5, or 6) can synergize to stimulate endothelial cells to express tissue factor (TF) and thereby provide a stimulus for coagulation system activation.^{16, 34} They further propose that this may provide for plasma extravasation and downstream activation of skin mast cells via protease activated receptors (PARs). This pathway could explain the rapid appearance of urticaria lesions in association with bacterial and other viral infections (see Figure 1 and review by Yanase¹⁶). The thesis, while novel, relates to the onset of the process but is unlikely to explain the chronicity that lasts months or years.

Serum factors

Another autoimmune theory is that CSU subjects express *autoreactive IgE* species that activate skin mast cells in CSU²⁷. One example is the idea that CSU subjects express elevated IgE to thyroid peroxidase³⁵. But we do not know whether such antibodies relate to the urticaria i.e. are they present in patients with Hashimoto's Thyroiditis (where IgG autoantibodies are 100% versus 25% for CSU) who have no urticaria. In fact, a clinical trial enrolling CSU patients carrying IgE to thyroperoxidase showed a marked clinical benefit in a time span of 1–2 weeks post the initial treatment with omalizumab and similar to that observed in Phase III studies³⁶. However, this rapid clinical response to omalizumab does not fit the known timing of omalizumab-induced reductions in allergen-mediated skin mast cell responses³⁷ or the timing of skin mast cell IgE receptors³⁸. This leaves open the validity of this proposed pathogenic autoIgE mechanism³⁹. More recently, a large scale study screening CSU serum for IgE reactive autoantigens identified IL-24 as a potential a disease-related autoantigen detected in a majority of CSU subjects' serum⁴⁰. However, the continuous presence of a skin autoantigen does not easily explain the waxing and waning nature of lesions or the locations of eruptions.

Coagulation cascade

As noted above, there is evidence for coagulation cascade activation in subjects with CSU^{41–44}. Damage to blood vessels can expose tissue factor and trigger the extrinsic cascade of events. Various activated elements of this coagulation cascade can activate PAR receptors on multiple cell types creating an amplification of pro-inflammatory mediators. Asero and his group showed that in patients with CSU, plasma levels of prothrombin fragment 1 fl 2 (PF1fl2), a polypeptide of about 34 kD, and D-dimer are higher than those in normal controls and correlate with disease severity and response to therapies. Tissue factor has also been noted in extravascular tissue beds and also in eosinophils found in CSU lesions⁴⁵. These observations are consistent with the mechanisms depicted in Figure 1. It should be emphasized that the product of intrinsic coagulation; namely thrombin, does not lead to blood clotting and that the same prothrombin fragment 1–2, and D-dimer are elevated in patients with hereditary angioedema where the mediator is bradykinin.⁴⁶ Mast cells, basophils, and eosinophils, have no known role in hereditary angioedema, and there is no urticaria. Activated endothelial cells may be the common denominator.

Several other serologic factors that can activate mast cells have been described. Bossi et al. demonstrated that human plasma from patients with CSU, but not that from healthy donors, induces histamine release from the human mast cell lines, LAD2 and HMC-1.⁴⁷ Asero et al. demonstrated the presence of histamine releasing factors with a molecular weight lower than 30 kD in patients with CSU.⁴⁸ Since such factors have not been purified therefore distinction from known basophil and mast cell activators such as C5a have not been demonstrated.⁴⁹ Histamine releasing chemokines are another possibility.⁵⁰

Basophils

Evidence has been mounting for the role of basophils in CSU pathogenesis^{51, 52}. Basophils carry IgE receptors and are capable of producing histamine, cytokines such as IL-4, IL-13, and IL-31 in response to IgE receptor activation^{53, 54}. Unique features noted in active CSU

patients are that blood basophils have reduced histamine degranulation in response to anti-IgE, basopenia⁵⁵, and basophil infiltration of skin wheals¹⁵.

Two distinct basophil functional phenotypes based IgE receptor triggered histamine release profiles have been described and termed CSU-Responder (CSU-R) (> 10 % release of total histamine content) and CSU- Non-responder (< 10 % release of total histamine content). The abnormal responsiveness appears to be due to elevated expression of intracellular phosphatases, which regulate IgE signaling pathways essential for histamine release, while other pathways for degranulation are unaffected (FMLP, MCP-1).^{56, 57} A recent study using flow cytometry to detect of CD63 induction on CSU basophils after IgE receptor triggering (also called the basophil activation test) confirmed the degranulation profile patterns of CSU R, CSU NR, and offered a third subset called CSU NR basopenic.⁵⁸ Earlier work has shown these functional phenotypes are stable during the course of disease⁵⁹. Improvement in basopenia and basophil IgE receptor abnormalities are seen in natural remission of CSU and points toward basophils as an important contributor to disease^{59–61}. Paradoxically, the blood basophils of patients who recover from CSU release more histamine when challenged through the IgE receptor that they did during active disease.

The number of basophils in peripheral blood is negatively correlated with urticarial disease symptoms activities,^{61–63} and suggests basophil recruitment to the skin contributes to skin symptoms. At present, recruitment pathways for basophils to skin lesions in CSU are unknown but the PGD2 pathway via the CRT2 receptor is implicated⁶⁴. Blood basophil activation in CSU is further supported by elevated activation marker expression which appears independent of autoimmune factors.^{65, 66} Evidence from the Phase III trials of omalizumab therapy in CSU show improvement in basopenia occurred in relation to the degree of clinical improvement and dose of omalizumab.⁶⁷ In addition, low baseline IgE and low basophil IgE receptors have been linked to poorer response to omalizumab.^{68–70}

Other cells and immunologic pathway

There is limited understanding of the roles for eosinophils, lymphocytes and neutrophils in disease pathology. A summary of altered immune pathways is provided in Table 1.

Future Considerations

Clearly the various aspects of pathogenesis require further investigation. While autoantibody titers may or may not reflect disease status (e.g. ANA's and rheumatoid factor do not, while c-ANCA levels do⁷¹), a role for IgG anti FcεRI alpha, in urticarial pathogenesis requires further clarification but does provide a mechanism for histamine release in those in whom it is present. While the latter is not more than 45%, the responsiveness of CSU to antihistamine therapy is no more than 50%. The “autoimmune” considerations based on a positive autologous skin tests or plasma factors that activate cells in vitro require identification of the agent responsible; otherwise its importance cannot be discerned. The hyporesponsiveness of patients' basophil seen in a substantial subpopulation of patients require factor investigation as to the mechanism(s) by which cellular phosphatases levels or modulated so as to distinguish an underlying defect in patients with CSU from one of many abnormalities due to the multiplicity of pathways that appears to be activated. The idea of

IgE antibody to any autoantigen needs further work regarding what such an autoantigen might be with appropriate controls for disease specificity, its location within skin, and distinction from a more general autoimmune response due to dysregulated B lymphocytes. The abnormalities of blood coagulation and the synergism of products as possible mediators of vascular permeability in CSU might be best approached by therapeutic manipulation of the putative agonist to determine the effect on severity of symptoms.

New therapeutic approaches may shed light on disease pathogenesis regardless whether they are being tried as a logical result of basic studies. Certainly, the effect of omalizumab is beyond anything that was originally considered. Possibilities might include antagonists of interleukin 5 (targeting eosinophils), dupilumab to target IL4 and IL13, antagonists to the CRTH2 receptor, blockade of PAR receptors, or anticoagulation with less toxic or cumbersome agents than heparin or warfarin.

Distinguishing Features of Chronic Spontaneous Urticaria vs Other Urticarias

Inducible urticarias are usually suspected based on the history⁷². In addition, there are particular characteristics that distinguish the appearance and duration of physically-induced hives from those of CSU. Individual lesions of cold urticaria, local heat urticaria, cholinergic urticaria, dermatographism, solar urticaria, and aquagenic urticaria are fleeting and last from a few minutes up to 2 hours⁷³. When biopsied, there is no cellular infiltrate. They respond to high dose antihistamines⁷⁴, and failing that to omalizumab^{75–77}, but do not respond to corticosteroid⁷³. The one exception is delayed pressure urticaria which has features resembling CSU. Individual lesions last from 4 hrs. – 24 hrs., there is a prominent cellular infiltrate⁷⁸, and it is responsive to corticosteroid usually requiring substantial amounts. They do differ in antihistamine responsiveness. For CSU, about half the patients have a satisfactory response to high-dose therapy³ while delayed pressure urticaria is typically unresponsive. Both delayed pressure urticaria and CSU can be treated with cyclosporine and omalizumab⁷⁹.

When dermatographism is very severe it can be confused with CSU. Some patients have pruritus much of the time and may have hives appear simply by clothing rubbing along the skin in the course of daily activities. Thus, it may appear to be “spontaneous”. Patients with CSU may, in addition, have symptoms of inducible urticarias. The most common associations are dermatographism and delayed pressure urticaria⁸⁰, thus all patients with CSU should be tested for dermatographism and questioned (or tested) about pressure-induced hives.

Diagnosis of CSU

In an otherwise health individual, very few tests need to be done for a proper evaluation. Skin testing for food allergy is not recommended^{1, 2}. The typical patient who suspects a food allergy as the cause may present with a lengthy list of suspected foods or has tried many different diets manipulations, none of which have made a consistent difference in clinical course. Laboratory tests are also kept to a minimum. A CBC with differential is helpful if

eosinophilia is seen. Then a stool for ova and parasites may be ordered. A sedimentation rate and/or CRP can help screen for autoimmune disorders, if prominently elevated, although the history and physical exam should suggest a more general problem. The ANA can be weakly positive, typically with speckled pattern if immunofluorescence is done, in about 30% of patients in the absence of systemic lupus erythematosus⁸¹. Thus, the test is often misleading and is not recommended as a routine screening procedure. Again, the suspicion of possible SLE is based on the history and physical exam.

The necessity (or lack thereof) of other tests is considered controversial. We do not test for helicobacter pylori; the evidence of an association is weak considering the prevalence of infection in the population-of-large. There is clearly an association of antithyroid antibodies (anti thyroglobulin and anti-peroxidase) with CSU^{82, 83} and some patients may be hypothyroid or even present taking thyroid hormone for prior hypothyroidism. Thus, ordering a TSH and anti-thyroid antibodies may indicate a predilection for autoimmunity. Nevertheless, current guidelines do not include these tests as requisite. As discussed in the next section, IgG antibody to the alpha subunit of the IgE receptor is an even more prominent indication of autoimmunity, but none of these tests affect one's choice of treatment.

Other diagnostic considerations, albeit uncommon ones, are urticarial vasculitis or an auto inflammatory disorder. Urticarial vasculitis is a different disorder; symptoms can include fever, petechiae, purpura, arthralgia/arthritis and occasional organ involvement such as renal disease^{84, 85}. There is elevation of the sedimentation rate and/or CRP, low C4 and C3, or proteinuria. Diagnosis requires a confirmatory skin biopsy which is not indicated for CSU. One particular subtype, hypocomplementemic urticarial vasculitis can be associated with a variety of systemic symptoms, has circulatory IgG antibody to C1q leading to very low C1q levels, and may respond to hydroxychloroquine as a steroid-sparing agent or canakinumab^{86, 87}.

Auto inflammatory disorders have urticarial-like rashes but the presence of fever and a positive family history are the most reliable indicators. These can include familial Mediterranean fever (FMF) cryopyrin-related disorders (cold-induced inflammatory syndromes) including familial cold urticaria (ice cube test negative) CINCA/NOMID syndrome and Muckle-Wells syndrome, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and hyper IgD syndrome (mevalonate kinase deficiency).^{88, 89} All respond to antagonists of interleukin 1 a common product of inflammasome stimulation^{90, 91}, although colchicine is first-line therapy for FMF. Schnitzler syndrome is also in this category but it, is not familial. This disorder is associated with monoclonal gammopathy (usually IgM), osteosclerotic changes, fever, and arthralgia or arthritis^{92,93}. Skin lesions are typically urticarial; papules or plaques may also be present, and on biopsy the perivascular infiltrate is neutrophilic compared to that of typical CSU.

Treatment of Chronic Spontaneous Urticaria

The treatment of this disorder has been virtually revolutionized with the discovery that omalizumab is effective even in the most complex, resistant cases⁹⁴. The earliest observation

was a case report of three patients⁹⁵ in which omalizumab was tried, and appeared to be successful. Since omalizumab was already approved for asthma, a typical “phase 1” study was not necessary. Instead a “proof of concept” study by Kaplan et. al.⁹⁶ unrolled 12 severe patients, all with evidence of autoimmunity (i.e. positive antibody to the IgE receptor some of whom had antithyroid antibodies) in a placebo-controlled, single-blind fashion. At the same time, an abstract appeared describing a double-blind, placebo-controlled study supported by Genentech at Johns Hopkins that demonstrated similar efficacy with 7 of 10 persons on active therapy achieving remarkable symptom control⁹⁷. In the Kaplan study, patients were unaware of the agent being administered and after a washout period, all received the placebo, and then were switched to omalizumab. During the 16-week study, 11 improved significantly and 7 were symptom-free. This led to a phase 2 trial of 90 patients led by Saini et. al. which was double-blind, and placebo controlled that confirmed striking efficacy and demonstrated effectiveness of doses of 150 mg or 300 mg⁹⁸. About that time, a study by Maurer et. al. was published in which patients were selected on the presence of antibody to thyroid peroxidase antigen³⁶. Similar results were obtained. While this last study postulated an allergic response to this thyroid enzyme as causative, there is no evidence of thyroid antigen being present in skin, and controls consisting of patients with Hashimoto’s thyroiditis without urticaria were not included. Nevertheless, the clinical result was clear. One thesis being promulgated at that time was the idea that removal of IgE by omalizumab would lead to down regulation of IgE receptors, hoping that too few would be present to allow cross-linking by IgG antireceptor antibodies. Thus, there was considerable focus on various immune or autoimmune mechanisms. But, it should be noted that the phase 2 study selected patients without regard to immune status and a separate small study, mirroring the “proof of concept” study, selected patients with no evidence of autoimmunity and the same efficacious results were obtained⁹⁹.

The final studies led to approval of Omalizumab for CSU for chronic idiopathic urticaria at dosages of 150 mg or 300 mg although the 300 mg dose was clearly superior. Each was double-blind, placebo-controlled and were designated Asteria I and II and Glacial^{100–102}. Each had over 300 patients, was double-blind and placebo-controlled, and strikingly similar efficacies were reported. A clear dose-response was noted between 75 mg (which did not reach statistical significance compared to the placebo), 150 mg, and 300 mg, but after 6 months of treatment, patients reverted to the level of control achieved in the placebo arm - - - interestingly, not to higher baseline level of symptoms. An important observation was the 25–30% placebo success rate in all three studies emphasizing the need for adequate numbers of patients in such trials and, the necessity of a placebo comparator. We surmise that the absence of these requirements relates to the large number of agents touted to have efficacy in CSU which over time have proven to be disappointing. In general, these phase three studies focused on patients who were resistant to antihistamines. Glacial differed in that 300 mg was the sole dose tested and patients failed H₁ receptor antagonists, H₂ receptor antagonists, and leukotriene antagonists. The overall success rate was 65–70% and 35–40% of patients had a complete response i.e. no pruritis, urticaria, or angioedema.

New guidelines are available¹⁰³ whose recommendations differ somewhat from prior iterations. There is no change; however, in the recommendation that second (or third) generation, relatively non-sedating H₁ antagonists, ought to be employed first, and high

dosage i.e. 4 times a day may be needed^{104, 105}. That approach had been shown years ago to be effective and safe for long-term use even when first generation antihistamines were employed¹⁰⁵. Now there is a major change - - - H₂ antagonists are not recommended and neither are leukotriene antagonists. In this aspect the new guideline approximates an earlier recommendation by Kaplan¹⁰⁶ that omalizumab should be employed first when patients are not satisfactorily responsive to antihistamines, and if they do not respond to omalizumab, cyclosporine ought to be the third choice. Current research is addressing questions as to when omalizumab might be discontinued, or how to taper the dose if and when a satisfactory response is obtained. Although approved (in the US) for 6 months duration, we know this is insufficient, population-wise, to result in remission, and even 1 yr. may not be enough.¹⁰⁷ However, if discontinued at 6 months and if symptoms recur, re-treatment is effective. Empirically, physicians are gradually increasing the interval between injections e.g. 5 weeks, then 6 weeks, and 8 weeks once good control is achieved. By contrast there is general agreement that if no response is obtained after 6 injections, the patient should be considered for cyclosporine¹⁰⁸. However, if a partial response is obtained, there is evidence that staying with therapy longer can lead to gradual improvement in symptom control^{108, 109}. Overall, quality of life indices of patients is markedly improved as a result of omalizumab therapy^{110, 111}.

Cyclosporine is considered third line even though its efficacy is almost as good as that of omalizumab, because it requires considerable more vigilance for possible adverse effects¹¹². Two early studies (one double-blind and placebo-controlled), demonstrated efficacy^{113, 114} and subsequent studies have been confirmatory^{115–117} as is the experience of investigators world-wide. The dosage for an adult is typically 200 mg/day (less than the dose typically employed for immune suppression i.e. 3.5 – 5 mg/kg) but if necessary can be tried at 250 mg or 300 mg as a maximum. Possible adverse effects are on blood pressure and renal function. Thus, it is recommended that those be normal at the outset and monitored every 4–6 weeks. Cyclosporine is commonly used by dermatologists as an alternative to methotrexate in the treatment of psoriasis or atopic dermatitis. One reason for its particular efficacy in CSU may be its ability to inhibit histamine release from basophils¹¹⁸ and mast cells¹¹⁹, an effect that is not seen with 6, mercaptopurine, azathioprine, methotrexate, or mycophenolate mofetil.

It has been estimated that the failure rate to all three drugs i.e. antihistamines, omalizumab, and cyclosporine, is about 7% i.e. 93% of patients can be successfully treated with these¹⁰⁶, however there is no specific recommendation as to what to do next. Agents considered in the past include sulfasalazine, dapsone, hydroxychloroquine, methotrexate, and intravenous gamma globulin. Any of these might be considered although the literature probably favors dapsone or sulfasalazine. While most publications regarding these alternatives are case reports, the few clinical trials published either lack a placebo group or have a placebo level which is falsely low, thereby inflating the apparent success rate.

Corticosteroids are not recommended for long-term use; the steroid side effects are proportional to dose and duration and over time cause more disability than the CSU. Nevertheless, a short course of steroid can be used to control acute symptoms until other modalities take effect. A typical approach might be 30 mg/day for 3 days and then taper by 5 mg each day for a total course of 8 days. Angioedema can be treated with 40 mg or 2 days

and then discontinue it without any taper. Although angioedema is much more difficult to assess over time because of its intermittent nature, omalizumab does decrease (or eliminate) the angioedema associated with CSU¹²⁰. Finally, although the mechanism of action of omalizumab is not yet clear, and more than one effect may be operable, patients seem to fail in two general categories; some responding quickly so that the first injection is ameliorative within a week (sometimes a few days) while others improve gradually over the initial 12 weeks of treatment^{109, 121}. The effects may relate to non-specific desensitization of cutaneous mast cells when IgE levels are markedly diminished, dissociation of cell-bound IgE from the IgE receptor, down-regulation of IgE receptors, normalization of basophil function and redistribution from the skin to the circulation, or elimination of IgE directly to an autoantigen that is yet to be deferred^{38, 39, 122–124}.

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Abbreviations

CSU	Chronic spontaneous urticaria
CIU	Chronic idiopathic urticaria
MrgX2	Mas-related gene X2
GPCR	G protein coupled receptor
TLR	toll-like receptors
PAR	protease activated receptors
CSU-R	CSU-Responder basophil phenotype
CSU-NR	CSU-Non- Responder basophil phenotype
CIndU	Chronic inducible urticaria

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Objectives

1. Update the recommendations for treatment of chronic spontaneous urticaria, particularly when unresponsiveness to antihistamines is encountered.
2. Review the progress made in elucidating the underlying abnormalities that contribute to the pathogenesis of chronic spontaneous urticaria.

Figure 1. Possible pathways that link coagulation cascade activation to bacterial infections. Taken from Yanase 2017 review¹⁶

Table I

Immune profiles of CSU subjects' relative to controls

Immune cell type/tissue	Profile
Lymphocytes	-Altered signaling through the p21Ras pathway ¹²⁵ -Increased frequency of IL-10+ peripheral T cells ¹²⁶ . -Detection of FcεRIα autoreactive T cells ²⁵
Peripheral blood mononuclear cells (PBMC)	-increased stimulated production of TNFα, IL-10, MIP-1α and RANTES ¹²⁷ -reduced IL-4 ¹²⁸
Peripheral blood dendritic cells (pDCs)	Impaired TLR9 induced interferon-α production ¹²⁹ .
Serum	Increase levels of TNF, IL-1β, IL-6, IL-13, IL-12p70, IL-10, IL-31 and B-cell activating factor (BAFF); similar among those with CSU and CAU ^{130–133} - Increased IL-6, CRP in CU subjects with NSAID sensitivity after aspirin challenge ¹³⁴
Coagulation	Extrinsic coagulation pathway activated with increased levels of D-dimer and prothrombin fragments ⁴¹ and appear to follow response to omalizumab ¹³⁵

Table II

Distinguishing feature of CSU from chronic inducible urticaria

Chronic urticaria	Diagnosis	Duration of lesions	Biopsy	Therapy
Inducible urticaria	History of a provocative stimulus- (cold, heat, pressure, solar, etc) Challenge by a challenge test to confirm suspected stimulus- ice cube test,	Most often lesions short-lived (minutes to 2 hours)	Biopsy without infiltrating cells *exception is delayed pressure urticaria which resembles biopsy in CSU	<ul style="list-style-type: none"> • Anti-histamines • Omalizumab
Chronic Spontaneous urticaria	History identifies a lack of a consistent trigger for the appearance of the majority of lesions Pressure is a common stimulus reported in CSU	4 to 24 hours	Mixed leukocyte infiltrate in a perivascular location	<ul style="list-style-type: none"> • High dose anti-histamines effective in 50% of cases • Omalizumab • Cyclosporin