

Treatment of Chronic Spontaneous Urticaria

Allen P. Kaplan*

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

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Chronic spontaneous urticaria is defined as persistent symptoms of urticaria for 6 weeks or more. It is associated with autoimmunity in approximately 45 percent of patients. Therapy is often difficult however the initial approach should employ high-dose non-sedating antihistamines; 4-6 tablets/day may be necessary. It has been shown that the response to 4 tablets/day exceeds 3, and exceeds 2, which exceeds 1. However the dose that corresponds to the maximal dose of first generation antihistamines (hydroxyzine, diphenhydramine) used previously, is 6/day. Yet over half the patients are refractory to antihistamines and other agents should be tried next. Whereas current guidelines (published) often add leukotriene antagonists and/or H₂ receptor antagonists next, these are of little utility. Likewise drugs effective for urticarial vasculitis (colchicine, dapsone, sulfasalazine, hydroxychloroquine) are effective in a small percentage of patients and no study suggests that the response rate of any of them exceeds the 30% placebo responses seen in most double-blind, placebo controlled studies. The drugs that are effective for antihistamine-resistant chronic spontaneous urticaria are corticosteroids, cyclosporine, and Omalizumab. Use of steroids is limited by toxicity. If used at all, a dose of no more than 10 mg/day should be employed with a weekly reduction of 1 mg. The response rates to cyclosporine and Omalizumab are each close to 75%. Cyclosporine can be used effectively if care is taken to monitor blood pressure, urine protein, blood urea nitrogen, and creatinine, every 6 weeks. Omalizumab has the best profile in terms of efficacy/toxicity and, once approved by federal agencies for use in chronic spontaneous urticaria, a dramatic change in the treatment paradigm, whether associated with autoimmunity or not, is predicted. A phase 3 trial is currently in place. Refractoriness to both Omalizumab and cyclosporine is expected to be less than 5 percent of patients. Other agents, can then be tried.

Key Words: Urticaria; anti IgE receptor; antihistamine; cyclosporine; omalizumab

INTRODUCTION

Urticaria is considered “chronic” when there is persistence of symptoms for over 6 weeks. However, terminology has evolved during the past decade and has become more specific. Early on, the physical urticarias were included within the rubric of “chronic” even though they are really intermittent and dependent on an encounter with some external stimulus. The term chronic “idiopathic” urticaria was also employed for decades, however we know a lot more about the etiology and pathogenesis of chronic urticaria, although experiments that “prove” a particular mechanism have not yet been achieved. Also there remains a large subpopulation of patients whose hives remain an enigma and can still be considered to be of unknown origin i.e. idiopathic. More recently, the term chronic spontaneous urticaria has been employed¹ to indicate chronic urticaria that is endogenous, and independent of any external physical stimulus, which is conceptually helpful, and does not imply knowing or not-knowing the cause. There is a clear association of a subpopulation of such patients (40%-45%) with autoimmunity who

are generally more severe, and therefore more difficult to treat.² Considerable pathogenic information is available and the term chronic autoimmune urticaria is often used by those of us who interpret the data as being causative or at least contributory in a substantial way. The non-autoimmune remaining 55%-60% of patients might still be considered to be idiopathic in that we have very little insight as to the cause or the pathogenesis. All these are “spontaneous”.

PATHOGENESIS

The key observations leading to an autoimmune designation

Correspondence to: Allen P. Kaplan, MD, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, USA.

Tel: +1-843-729-0264; Fax: +1-843-722-1253; E-mail: kaplana@musc.edu
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for many patients with chronic spontaneous urticarial have been recently reviewed in considerable detail² and will be summarized only briefly herein. Patients were found to be autoreactive to their own serum,³ now employed as the autologous skin test.⁴ Although both sensitivity and specificity of this test is limited, most patients who react to their own serum to produce a wheal and flare reaction upon intradermal skin test, are responding to an IgG immunoglobulin with a positive incidence of about 30%. Soon thereafter, reports appeared indicting that an occasional patient (5%-10%) has circulating IgG anti-IgE that is functional and can activate donor basophils to release histamine.^{5,6} Next, a much larger number of patients were found to have IgG antibody directed to the IgE receptor α subunit.⁷ This autoantibody was functional on skin mast cells and basophils^{8,9} and can be an initiating stimulus for hive formation. It is important to note that the IgG of many such patients was purified and shown to possess this reactivity,⁹ even though most routine assays employ whole serum with no further molecular characterization. Saturating IgE receptors with myeloma IgE blocked the ability of patients' anti receptor antibody to degranulate basophils,¹⁰ and the histamine release was augmented by serum complement.¹¹ This was subsequently shown to be due to activation of the classical complement pathway and the augmentation was eliminated by employing C5-deficient serum added to purified patient IgG¹² or by adding antibody to the C5a receptor to patients' sera prior to assay. Thus considerable molecular evidence exists regarding the function of these autoantibodies. When histamine release is employed as the assay, positive tests rarely occur in normal subjects, or in other urticarial disorders, or in autoimmune disorders. In one assay we reported 54 positives in 104 patients with chronic spontaneous urticarial and none in 35 allergic patients lacking urticaria.¹³

It is important to note that binding assays (enzyme-linked immunosorbent assay [ELISA], immunoblot) for anti IgE receptor antibodies employing cloned α subunit give false positives and likely accounts for the non-specificity reported.¹⁴ In one of the original reports of positive antibodies to the IgE receptor in patients with autoimmune diseases such as pemphigus and dermatomyositis, the authors were unable to demonstrate any histamine release even though positive ELISA assays or positive immunoblots were observed.¹⁵ Histamine release was observed only in the patients who had chronic urticaria. Other published reports are similar.^{16,17} When we attempted to develop an ELISA binding assay to substitute for basophil histamine release, we failed because positives were found in virtually everyone¹⁸ even when the assay was made specific to IgG₁ and IgG₃ subclasses. The latter subclasses are the major ones that fix complement and account for most of the histamine-releasing activity.¹⁹ In fact IgG₂ antibodies to the IgE receptor α subunit were found by binding assay and not by histamine release in patients whose IgG₁ and/or IgG₃ clearly caused histamine secretion.¹⁹ This is consistent with recent observations that the non-specific reac-

tivity is due to antibody binding to the insect carbohydrate attached to the human α subunit since it was originally cloned employing an insect vector.²⁰ Such binding does not lead to IgE receptor perturbation requisite for histamine release.

Additional observations regarding pathogenesis include decreased responsiveness of patients basophils to rodent anti IgE due to elevated phosphatases,²¹ activation of the extrinsic coagulation cascade based on the presence of activated Factor VII, thrombin fragments, and fibrin split products,^{22,23} as well as elevated levels of metalloproteinase 9²⁴ and vascular endothelial cell growth factor. The relation to disease pathogenesis is unclear although the aforementioned basophil abnormality reverses upon urticaria-remission or successful therapy.²⁵

TREATMENT

Numerous guidelines are available^{1,26,27} to assist physicians in treating patients with chronic spontaneous urticaria. The mainstay of initial therapy is clearly high-dose antihistamines and patients can be divided into those that are antihistamine responsive and those who are not. The number of alternatives to antihistamines is large but the evidence of efficacy for most of them is weak. On the other hand, some of the new approaches are extremely effective and have the potential to radically change the approach to treating this often frustrating disorder.

Antihistamine responsive patients

Antihistamines are effective in treating 45%-60% of patients; the remainder are refractory and achieve little or no benefit even from maximal doses. This is not surprising because chronic spontaneous urticaria should not be viewed as a disorder mediated by histamine secretion any more than rhinitis or asthma are histamine mediated. Clearly histamine is a major contributor, but allergic or allergic-like disorders characterized by a prominent cellular infiltrate (either a late-phase reaction or comparable inflammatory response) often require additional approaches. The frequent requirement for corticosteroids to treat allergic rhinitis or asthma is a testament to that proposition, and the cellular infiltrate that characterizes chronic urticaria²⁸⁻³⁰ (a non-necrotizing perivascular infiltration of CD4+ lymphocytes, monocytes, neutrophils, eosinophils, and basophils) falls into that category. By contrast, dermatographism is an example of a histamine-mediated urticaria i.e. we know of no other mediator, there is no significant cellular infiltrate, and no evident late-phase reaction once the wheal and flare reaction subsides. It responds to antihistamines but not to steroid.

Responsiveness to antihistamines is dependent on occupancy of H-1 receptors. These drugs are inverse agonists that lock the H-1 receptor into an inactive conformation. Histamine shifts the receptor equilibrium to an active conformation leading to vasodilatation and increased vascular permeability. Thus although antihistamines do not compete with histamine for

binding to the H-1 receptor, as would a competitive antagonist, they do compete regarding the receptor conformation equilibrium. Thus, histamine released into the skin can lead to histamine-induced receptor effects even in the face of antihistamine therapy when the antihistamine receptor occupancy, based on the dose taken, is too low. The antihistamine will then be ineffective. That is the reason why the typical once-a-day second generation “non-sedating” antihistamine used to treat allergic rhinitis often fail to be effective in the treatment of chronic urticaria. The fact that innumerable studies of these drugs show that one/day is better than placebo,³¹⁻³⁵ although true, is misleading because the benefit accrued, but for the mildest of patients, is too low to be of significance in terms of patient symptom relief or quality of life when the disease is moderate to severe.

This became apparent recently with the study of cold urticaria,³⁶ a predominantly histamine-mediated urticaria, where 4 tablets per day was more effective than 3 tablets per day which was more beneficial than 2 or 1 tablet per day. This comes as no surprise although it was presented as conceptually new. The prior drug of choice was cyprohaptadine,³⁷ a first generation antihistamine that is dispensed as 4 mg tablets and 4-8 tablets/day was required to treat most cold urticarial patients.³⁸ Although chronic spontaneous urticarial has a lesser response to antihistamine and is a far more complex disorder, the same scenario of 4 tablets/day being better than lesser quantities³⁹ was found. This too, is not new. For example, 4 cetirizines/day is equal to 25 mg of hydroxyzine taken 5 tablets/day and the dose of hydroxyzine found to be effective for chronic urticaria patients varied from 100-200 mg/day⁴⁰ in divided doses. Although not tested in a blinded or placebo controlled fashion, the same increasing responsiveness (in those responsive to antihistamines at all) was noted, and the patient number exceeded 10,000 over 35 years.⁴¹ By this analysis, a dose of 6 cetirizines/day would be predicted to be maximal for the most severe, but still responsive patients.

The choice of antihistamine to be used favors the second generation agents which have been studied to a much greater extent than first-generation agents and are more specific for the H-1 receptor and have a better side-effect profilé.⁴² For example they have less sedation, and less likely to cause dry mouth, do not cross the blood-brain barrier to any appreciable extent (fexofenadine may be the only one that is truly zero), do not effect REM sleep, etc.⁴³ Thus it is assumed that long-term therapy with first generation agents, even if equally effective as second-generation agents for treatment of chronic spontaneous urticaria, would lead to poor performance at work or at school, auto accidents, etc.

Although first generation agents were used successfully for decades before second-generation agents became available, guidelines emphasizing use of second-generation agents as a routine now, seems appropriate.¹ However data demonstrating

harmful side effects when first-generation agents are used chronically in patients with chronic spontaneous urticaria do not exist i.e. the conclusion may be correct but the reasons given, may be incorrect or at least substantially exaggerated. My opinion, previously published⁴¹ is based on extensive experience employing first generation agents with therapeutic success and very few side effects. The issue is that side effects of first-generation agents has not been assessed in chronic urticaria patients, but extrapolated based on what has been observed in normal subjects or those with other allergies. Second, the duration of such studies is relatively short i.e. usually a few days, and often just one or two doses of an antihistamine such as diphenhydramine is reported. But if side-effects are most prominent in the first few days and dissipate over a week, could they not be employed if the duration of therapy varies from 3 months to 2 years? Is there CNS tachyphylaxis over time (which requires crossing the blood-brain barrier)? Is the non-specificity of first-generation antihistamines helpful because of some of the additional receptor-mediated effects? These questions can be answered only by a direct comparison of high-dose therapy in patients with chronic urticaria employing closely related agents such as cetirizine vs. hydroxyzine each of which is known to be efficacious.

Antihistamine refractory patients

High dose antihistaminics (H1 receptor “antagonists”) are effective in 45%-50% of patients and no other therapy is required other than tapering the dose as the patient improves. However refractory patients require addition or substitution of alternative agents. These are listed in Table; the left side includes those that are in the literature and are included in most guidelines while the right side lists only 4 (3, not including antihistamines) which are the only ones that I believe to be efficacious in a large percentage of histamine-refractory patients.

The newest and most promising approach to the treatment of refractory patients is the use of Omalizumab. A phase one trial,

Table. Therapeutic choices

Antihistamines	Antihistamines
First & Second Generation	First & Second Generation
H ₂ -receptor antagonists	Corticosteroid
Leucotriene antagonists	Cyclosporine
Hydroxychloroquine	Omalizumab
Dapsone	
Colchicine	
Sulfasalazine	
Cyclosporine	
Omalizumab	

Choices of therapies for treatment of chronic spontaneous urticaria. The column on the left lists most drugs commonly employed. The list on the right includes only those agents to which most patients respond. The response rate to antihistamines is 45%-50% and the response to corticosteroid (low-dose), Omalizumab, and cyclosporine are each about 70%-80%.

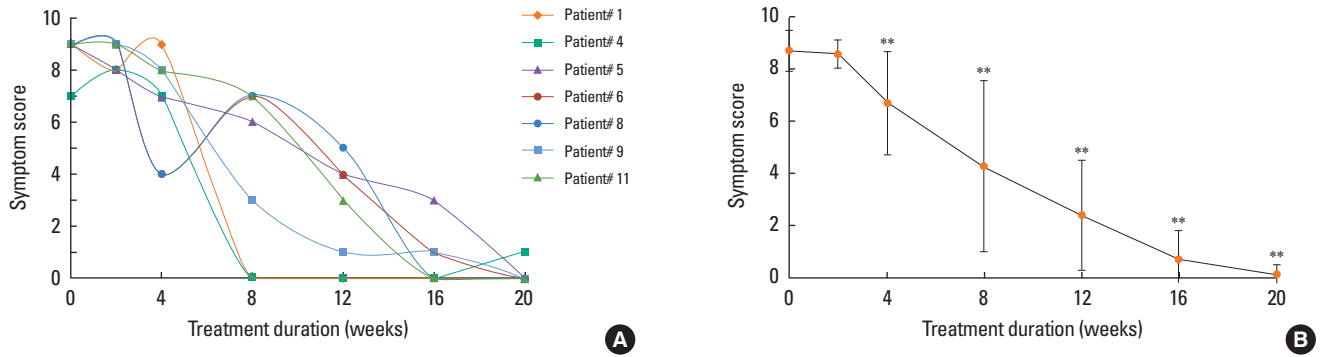


Figure. (A) Response of 7 patients to Omalizumab demonstrating progressive relief of symptoms, all of whom remit between 1 month and 4 months of a monthly injection. In this study, 4 additional patients improved, but did not remit, and one did not respond. (B) Composite symptom score for patients showing the mean and standard error at each time point. A significant difference is noted by 4 weeks.

single blinded, and placebo controlled revealed a success rate in 11 of 12 patients with 7 of them achieving remission.⁴⁴ The data are shown individually in Figure. A phase 2 trial included 80 patients and revealed the same result with a response rate of over 75% many of whom improved dramatically.⁴⁵ The former study chose particularly severe patients with chronic autoimmune urticaria. All had IgG anti IgE receptor antibodies and many also had antithyroid antibodies. The latter study employed patients with chronic spontaneous urticaria; the presence or absence of autoimmunity was not assessed. Many other case reports attest to the efficacy of Omalizumab⁴⁶⁻⁴⁹ and one study employed patients without autoimmunity with virtually the same response rate.⁵⁰ Two aspects of these studies indicate that IgE anti receptor antibody is not necessarily a cause of chronic urticaria, even in a subpopulation of patients. The response in those lacking autoantibodies is unexplained, while the response in those with IgG anti IgE receptor antibody is often so rapid that time sufficient for downregulation of the IgE receptor (as IgE levels plummet) has not transpired. A non-specific, rapidly occurring down-regulation of mast cell secretion is suggested.

Cyclosporine has been shown to be effective in the therapy of severe chronic urticaria unresponsive to other modalities in two double blind, placebo-controlled trials.^{51,52} Experience has substantiated these optimistic results with a response rate of 75%-80%. The average dose for an adult is 200 mg/day (3-3.5 mg/kg); occasional patients may require 250 mg or even 300 mg but we have never exceeded this dose. After a few quiescent months, it can be tapered at 50 mg/month down to 100 mg/day and then 25 mg/month. Cyclosporine has side effects that require monitoring including effects on blood pressure and renal function. We suggest a blood urea nitrogen, creatinine, urinalysis, and blood pressure check at the start of therapy and every 4-6 weeks thereafter. Thus it is contraindicated in patients with hypertension or renal dysfunction but can be employed in diabetics who have normal renal function where steroids would be contraindicated.

The most common drug used to treat severe chronic sponta-

neous urticaria is corticosteroid. Unfortunately high doses are commonly employed for protracted periods of time. Although there are no recent studies of efficacy, there is no question that patients respond. However guidelines recommend short term use for acute urticarial episodes, but do not recommend sustained use because of the risk of side effects including weight gain, hypertension, osteoporosis, cutaneous striae, cataracts, and altered fat distribution. There is no question that chronic, high-dose steroids should not be used to treat chronic urticaria. However in precluding sustained use, one potentially effective approach has been eliminated. Prior to the advocacy of cyclosporine or Omalizumab, we recommended alternate day steroid at 20-25 mg every other day which averages 10-12.5 mg each day and more recently, favor daily use starting at 10 mg/day. If a daily approach is employed, a considerable lessening in symptoms often is seen and the dose can be tapered at 1 mg/week. This is an effective, safe approach so that the duration of steroid use averages about 3 months, with the dosage gradually decreasing. When steroids were originally employed for autoimmune diseases such as rheumatoid arthritis, high daily doses were employed, and side effects were considerable. Their utility was questioned because long-term side effects exceeded any benefit. However low-dose steroid treatment was later employed with much greater utility. Even now when methotrexate plus potent biologic agents are employed, steroids have been found to be effective at the 5-10 mg/day range⁵³ and can be used for years with severe side-effects averted even though rheumatoid arthritis is associated with periarticular osteoporosis. There is no reason why we cannot use corticosteroids in a rational way for chronic spontaneous urticaria. At present, Omalizumab is not approved by the FDA in the USA for use in chronic urticaria and the situation worldwide is likely similar. If a histamine refractory patient cannot take cyclosporine, the agent with the greatest response rate is low-dose corticosteroid.

The list on the left side of Table includes H₂ receptor antagonists and leukotriene antagonists. The literature regarding these agents is of dubious quality, involving relatively small numbers

of patients, and they are more often prescribed as additives to H-1 receptor antagonists, than used individually. Experience with them has been generally disappointing. If the patient is unresponsive to high-dose H-1 antihistamines, adding these is unlikely to create a responsive individual. Other agents such as dapson, colchicine, and hydroxychloroquine were originally suggested for urticarial vasculitis, a totally different disorder from chronic spontaneous urticaria, so that reasoning that an effect on one will necessarily lead to a positive response in the other is erroneous. Actual studies of these drugs are limited so that there is little convincing evidence that they work. None of these drugs have been studied in a double blind placebo-controlled fashion in a large enough group of patients with a response rate that exceeds the 30%-35% response to placebo. None of these achieve that level of response. Sulfasalazine is favored by some since it is effective in some arthritics and is a major agent for ulcerative colitis where 5 amino-salicylic acid is the active moiety. The best study of this agent lacks a control group⁵⁴ and I am reluctant to treat hives with a sulfa compound and an aspirin derivative.

SUMMARY

The reliable drugs for the treatment of chronic spontaneous urticarial are antihistamines, Omalizumab, cyclosporine, and low-dose corticosteroids. With these agents, only a rare patient remains refractory and avoidance of the other agents listed in Table saves considerable time, cost, and frustration.

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