

Treatment of Patients with Chronic Idiopathic Urticaria

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Abstract

Treatment of patients with chronic idiopathic urticaria (CIU) involves reducing symptoms with the least invasive therapy and carefully balancing risk and benefit. The mainstay of therapy is the use of antihistamines with or without the use of intermittent pulses of corticosteroids. Alternative therapies to chronic corticosteroids include leukotriene antagonists, plasmapheresis, dapsone, stanazolol, hydroxychloroquine, methotrexate, cyclosporin, tacrolimus, and warfarin. A practical approach to CIU bases treatment and severity on the patients' previous response to therapy. Therapy goals are to reduce symptoms until spontaneous resolution occurs. Management of CIU patients can be both frustrating and rewarding.

Index Entries: Urticaria; hives; therapy; treatment.

Treatment of chronic idiopathic urticaria (CIU) is usually palliative rather than curative (1). Long-term treatment is typical for the patient with CIU, which usually persist for months to several years with relapsing exacerbations.

General Measures

Nonspecific aggravating factors, such as overheating, stress, alcohol, and drugs that have the potential to worsen urticaria should be minimized. In general nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in aspirin-sensitive urticaria patients. Angiotensin-converting enzyme (ACE) inhibitors should be used with caution in patients with concurrent angioedema. Patients with minimal urticarial lesions may use cooling antipruritic lotions such as 1% menthol in aque-

ous cream, and calamine lotion. Clearly written handouts prepared for the patient by the physician, or information provided by the American Academy of Allergy, Asthma and Immunology or the American College of Allergy, Asthma and Immunology, can help patients to better understand their disease. In the treatment of patients with urticaria, it is crucial to explain the many causes of hives and to enlighten the patient about the concept of CIU.

Epinephrine

Intramuscular or subcutaneous epinephrine can be life-saving in anaphylaxis and upper-airway angioedema associated with acute allergic reactions or severe exacerbations of chronic urticaria. Epinephrine should be used with caution in hypertension and ischemic heart disease. Dosing is weight-dependent. The current recommendation is 0.3 cc of a 1:1000 solution of epinephrine given by intramuscular injection for adults and adolescents. Children should be given 0.15 cc of the 1:1000 solution. If there is no effect after the first dose of epinephrine, the dose should be repeated. Epinephrine is not effective for angioedema caused by C1-inhibitor deficiency. Oral beta adrenergic agonists have limited benefit for acute or chronic urticaria.

Antihistamines

Antihistamines are the mainstay of symptomatic management in CIU (2–4). The diversity of other mediators and cytokines and the participation of inflammatory cells in chronic urticaria explains why antihistamines do not always completely eliminate all the signs and symptoms of chronic urticaria. Antihistamines should be prescribed on a daily schedule in sufficient doses achieve and maintain a cutaneous antihistamine effect. Sedation is a limiting side effect of most classical antihistamines, but may be beneficial to some patients who have difficulty sleeping because of pruritis. Anticholinergic side effects of older antihistamines including dry mouth, urinary retention, and blurred vision, may limit their use. Tolerances for side effects may be achieved over time or by prescribing low doses initially and increasing the dose gradually.

Three low-sedating H₁-receptor antagonists are currently licensed for urticaria in the United States. Classic sedating antihistamines have the potential to promote sedation and to interfere with central nervous system (CNS) reflex reaction times and globally suppress the CNS-suppressive effects comparable to those of alcohol (5–8). Fexofenadine, ceterizine, and loratadine are less sedating antihistamines, which are available in the United States to treat urticaria. Optimal starting doses

for loratadine is 10 mg and for fexofenadine is 60 mg twice daily (9). Cetirizine had a greater duration of antihistaminic activity in the skin over a period of 24 h than fexofenadine (10). Many physicians use the combination of fexofenadine (180 mg), loratadine (10 mg), or cetirizine (10 mg), with an effective nighttime dose of an antihistamine such as hydroxyzine. None of these less sedating antihistamines have been associated with the side effect of torsades de pointes, as reported to occur with terfenadine and astemizole. The addition of an H₂ antagonist may offer better control of urticaria, particularly pruritus, than an H₁ antagonist alone (11). It is common practice to double the dose of the less sedating antihistamines. Cetirizine and loratadine, when used in in vitro studies, have mast-cell-stabilizing effects that may be of clinical importance, especially at higher doses (12,13). Both medications can cause sedation at increased doses. The dose of fexofenadine can be increased without the concern of sedation. Studies have addressed the issue of sedation and safety with fexofenadine up to 800 mg per d as a single daily dose, adding up to 690 mg twice daily for 1 mo (14). The prescribing of sedating antihistamines—such as hydroxyzine—as monotherapy is now less common because of concerns about reduced cognitive functions, but this class of antihistamine is effective and well-tolerated by many CU patients.

Doxepin is a tricyclic antidepressive medication, which has very potent H₁- and H₂-antagonist capability (15). This drug is particularly sedating, and therefore is best used as a nighttime dose of 10–75 mg to supplement a nonsedating antihistamine used in the morning. Higher doses may be used, but side effects increase substantially as the dose is increased. Sedation may be very beneficial to the patient when sleep deprivation is observed. However, doxepin is metabolized by the cytochrome P450 enzyme system, and care should be taken to avoid concurrent administration of other drugs that are similarly metabolized.

Antihistamines in Pregnancy

If possible, it is best to avoid all antihistamines in pregnancy, especially during the first trimester, although none have been shown to be teratogenic in humans. Both loratadine and cetirizine have pregnancy category B ratings. Fexofenadine has a category C rating. All antihistamines should be avoided in pregnancy and breastfeeding if possible. Chlorpheniramine and diphenhydramine may be used in pregnancy because of their long safety profile.

Antihistamines in Childhood

None of the antihistamines are contraindicated in children over 12 yr of age. The second-generation antihistamines cetirizine and loratadine have FDA-approved indications down to age 2 and 3, respectively.

Diphenhydramine is often used as an over-the-counter medication by parents, and this antihistamine is considered safe for the young chronic urticaria patient.

Leukotriene Antagonists

Leukotriene modifiers should be considered as alternative therapy for patients with CIU. These medications include the leukotriene antagonists zafirlukast and montelukast and the 5-lipoxygenase-enzyme-inhibitor zileuton. Case reports indicate their value in conjunction with antihistamine therapy for the management of chronic idiopathic urticarial (16,17). To date, there are no double-blind, controlled studies using leukotriene-receptor antagonists in the treatment of urticaria. In clinical experience, patients often respond to leukotriene antagonists. These agents may have a role as an add-on treatment along with antihistamines, or as a steroid-sparing agent.

Mast-Cell-Stabilizing Drugs

Drugs with mast-cell-stabilizing properties are not licensed for urticaria. Ketotofen has been used for its antihistaminic properties, but is sedating and not currently available in the United States (1). Nifedipine has been shown to reduce pruritis and whealing in CIU, presumably by modifying calcium influx into cutaneous mast cells, but the overall clinical benefit is often disappointing (18). Oral sodium cromoglycate has not been an effective treatment for chronic urticaria, but some patients with mastocytosis may benefit from this drug.

Corticosteroids

The role of systemic corticosteroids in the treatment of CIU should be limited because of the side effect profile. Tapering courses can be very useful when rapid control is needed or when exacerbations of chronic urticaria occur. Long-term oral corticosteroids should not be used in chronic urticaria except in highly selective cases, and only with a specialist's supervision. Problems encountered with long-term therapy include systemic toxicity such as Cushingoid characteristics and osteoporosis and exacerbations of chronic urticaria when attempting withdrawal, plus the withdrawal syndrome from corticosteroids.

Corticosteroids are very effective in suppressing most of the signs and symptoms of CIU. The exact pharmacologic action in chronic urticaria is not fully understood. The steroid molecule enters the cell after forming a complex with its receptor, which then enters the nucleus. Subsequently, the inhibition of gene expression and coding for messenger RNAs for the synthesis of pro-inflammatory interleukins and cytokines may suppress the cutaneous process involved in chronic urticaria.

Corticosteroids should only be used in the most severe, refractory CIU cases and during uncontrolled exacerbations of chronic urticaria and angioedema. Corticosteroid side effects can be significant, particularly in high doses and for extended periods (19). In most cases, the severity of the disease dictates the dose of the corticosteroid that is required to maintain symptom relief. Treatment of CIU usually requires months to several years of therapy. The use of corticosteroids for this duration would be complicated with side effects. Some patients perceive the corticosteroids are the most effective treatment and “the only medication that works.” This type of patient would be very reluctant to stop corticosteroids, either because of the severity of their CIU, or because of the fear of having an uncontrollable exacerbation. The patient must be given a schedule for tapering the corticosteroids. Complete withdrawal of the corticosteroid is the main objective, unless clinical worsening occurs at a low dose. In Kaplan’s (20) experience, corticosteroids can usually be discontinued after 3 mo. Initially, prednisone (40 mg every day) is prescribed and then tapered to an alternate-day schedule—such as 25 mg every other day while the urticaria remains in remission—and slowly tapered over the ensuing months. In extreme cases of CIU and angioedema (20) and in the cases of delayed-pressure urticaria (DPU) that only responds to corticosteroids (21), the potential to become corticosteroid-dependent is high. These patients need constant reassessment and monitoring. The goal in the management of these patients is to use the lowest effective dose—preferably an alternate-day regimen of corticosteroids—and continue maintenance antihistamines and use of steroid-sparing drugs.

Immunomodulatory Therapies

Plasmapheresis was evaluated in eight patients with CIU who were identified to have histamine-releasing autoantibodies (22). Symptoms were abolished for 2 mo in one patient and for 3 wk in another. Two patients had complete resolution of urticarial symptoms, and two others had only temporary relief. Two subjects had no symptom relief. Therefore, plasmapheresis may be effective as a treatment for some chronic autoimmune urticaria patients, but the cost is prohibitive. Intravenous (iv) immunoglobulin was studied in 10 patients with severe autoimmune chronic idiopathic urticarial (23). All patients had evidence of serum histamine-releasing autoantibodies. Clinical benefit was noted in 9 of 10 patients: three patients continued in prolonged complete remissions have 3-yr follow-up, two had temporary complete remissions, and symptoms in four patients improved following treatment. Intravenous immunoglobulin is a therapeutic option for patients with recalcitrant chronic autoimmune urticaria, but the cost is prohibitive and the treatment has inherent risks.

Dapsone, stanazolol, hydroxychloroquine, and methotrexate are anti-inflammatory therapies that may be utilized in patients who have CIU and require long-term corticosteroids (3). Stanazolol (24) was studied in three steroid-dependent women with CIU, and methotrexate (25) in one individual requiring chronic corticosteroids. Success with use of dapsone (26) and hydroxychloroquine (27) in patients with steroid-dependent chronic urticaria have been reported. In these difficult cases, all attempts to taper or to utilize alternate-day corticosteroid therapy is mandatory. The response to a month-long clinical trial for each one of these drugs is unpredictable in the individual patient, and side effects must be monitored. Some patients have good responses, and corticosteroids can be withdrawn—which justifies an open clinical trial. These drugs remain unproven as effective treatments for chronic urticaria until large, double-blinded clinical trials have been conducted.

Cyclosporin, used as an immunosuppressant in organ-transplant patients, has been demonstrated to inhibit cell-mediated immunity by downregulating Th₁ lymphocyte responses, and T-cell-dependent antibody formation by B-lymphocytes (18). Cyclosporin has inhibitory effects on anti-IgE-induced histamine release from human basophils and skin mast cells in vitro (28). Thirty patients who had severe, daily, or frequent CIU were enrolled in a 4-wk study evaluating the effects of cyclosporin therapy vs placebo (29). Nineteen patients were randomized to receive active drug, and 10 patients were randomized to receive placebo. Patients were continued on cetirizine therapy at 20 mg daily throughout the study. Cyclosporin was dosed at 4 mg per kg daily. Dosage adjustments were made based upon serum creatinine, serum potassium, total serum bilirubin, or liver-enzyme elevation, or elevation in diastolic blood pressure. Eight of the nineteen on active treatment but none on placebo had responded at 4 wk ($p < 0.05$). Three others on active drug met the criterion for response at 2 wk but not at 4 wk. Seventeen nonresponders (seven randomized to active and 10 to placebo) chose open-labeled cyclosporin, and eleven responded after 4 wk. Six of the eight randomized active drug responders relapsed within 6 wk. Of the nineteen responders to randomized and open-label cyclosporin, five had not relapsed by the study end point (24 wk). Side effects during cyclosporin treatment were common, but not severe enough to require withdrawal from the study. Cyclosporin is an effective treatment for some CIU patients who are unresponsive to traditional therapy. The treatment is unsuitable for patients with risk factors related to malignant disease, such as a strong family history or personal history of cancer.

Tacrolimus is an anti-inflammatory therapy used in organ-transplant patients. Tacrolimus is approved to be applied topically for young, atopic dermatitis patients. Tacrolimus inhibits T-cell activation, thereby reducing the expression of multiple cytokines involved in inflammation (30). Tacrolimus was recently found to significantly and

Table 1
An Approach to the Treatment of Chronic Urticaria

Mild—complete control obtained with low-sedating anti-H1 therapy	
Begin with a low-sedating antihistamine (H1) QD to BID	
a. Claritin (loratadine)	10 mg qd-bid
b. Allegra (fexofenadine)	60–180 mg qd-bid
c. Zyrtec (cetirizine)	10 mg qd-bid
Moderate—incomplete control with low-sedating anti-H1 therapy	
• Begin with high doses of sedating antihistamines • Use combination of low-sedating anti-H1 in the AM and sedating anti-H1 in the PM • Add leukotriene antagonist • Add anti-H2 therapy • Use short courses of oral corticosteroids: a. hydroxyzine 50 mg qhs to qid b. doxepen 10–50 mg as a single nightly dose, up to 75 mg bid for a 1-mo trial c. singulair 10 mg qhs-bid, accolate 20–40 mg bid, or Zyflo 600 mg qid d. ranitidine 150–300 mg bid e. prednisone 6-day (60,50,40,30,20,10 mg) or 12-day courses (60,60,50,50,40,40,30,30,20,20,10,10 mg)	
Severe—poor response to anti-H1 therapy, requires frequent use of corticosteroids	
• Continue high-dose antihistamine • Add long schedule of tapering corticosteroid • If unable to taper off prednisone or unacceptable side effects, utilize steroid-sparing/immunomodulating drugs, initially dapsone 25–50 mg bid, hydroxychloroquine 200 mg bid or methotrexate 5–15 mg weekly for 4-wk trial • For refractory, steroid-dependent cases: a. tacrolimus: start at .05 mg/kg/d up to .2 mg/kg/d in divided doses, start with 1 mg bid, or b. cyclosporin start at 4 mg/kg/d, start with 25–100 mg daily	

dose-dependently inhibit the release of histamine and leukotrienes following antigen stimulation, whereas dexamethasone did not (31). In the same study, tacrolimus was also found to dose-dependently inhibit degranulation of mast cells, and dexamethasone did not. Both tacrolimus and dexamethasone significantly inhibited TNF alpha and IL-5 protein production as well as mRNA expression. Tacrolimus has been found to be more powerful in the inhibition of cytokine production and release of chemical mediators than steroids, suggesting that this immunosuppressive drug may be useful for the treatment of inflammatory conditions such as asthma and chronic urticaria. Trials with tacrolimus (Prograf) in patients who had corticosteroid-dependent CIU resulted in good to excellent results. Doses between .05 and .2 mg per kg per day in twice-daily schedule were used. Monitoring renal and liver function is necessary. A tacrolimus blood level should be obtained. Blood levels should

be maintained under 20 ug/mL to prevent toxicity. Side effects in general have been less than that seen with cyclosporin therapy.

Other Interventions and Treatments

Thyroxine treatment of euthyroid patients with CIU and with evidence of thyroid autoimmunity may lead to remission of urticaria (32). Although some immediate benefit from using very potent topical steroids under occlusion for chronic urticaria has been reported (33), the use of topical corticosteroids is not recommended.

A recent study has demonstrated that warfarin may be beneficial in treating patients with CIU (34). A double-blind placebo-controlled crossover study found six of eight CIU patients had a dramatic response with reduction of pruritis and angioedema. The mechanism of action (MOA) is unclear, and requires further study.

Summary

The management of CIU can be very frustrating for both the expert physician who treats *chronic urticaria patients* and the patient. Table 1 outlines a treatment approach for the management of CIU. The severity of CIU is based on clinical course and response to previous therapies. Medications are therefore selected for the appropriate level of severity. The goal of therapy is to provide chronic urticaria patients with relief of symptoms along with minimal side effects from prescribed treatment until spontaneous resolution occurs. The treatment of chronic urticaria may not hasten the resolution.

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