

Treatment of Refractory Chronic Urticaria: Current and Future Therapeutic Options

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Abstract Chronic urticaria is a distressing disease that affects up to 1 % of the general population at a time point in life and may severely worsen the quality of life. First-line treatment has been based on antihistamines, and presently relies on the use of non-sedating, second-generation antihistamines; following the recommendations of the recent international guidelines, in patients who do not respond to antihistamines at licensed doses, the daily dosage of these drugs can be increased up to fourfold. Nonetheless, a significant proportion of patients with chronic urticaria remain poorly controlled; in these cases, alternative therapeutic approaches have to be considered. This article critically reviews all of the third- and fourth-line treatment options suggested for patients whose disease is refractory to antihistamines, including systemic corticosteroids, leukotriene receptor antagonists, several different anti-inflammatory drugs (dapsone, sulfasalazine, hydroxychloroquine), various immunosuppressive drugs (calcineurin inhibitors, methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil), intravenous immunoglobulin, and newer treatment options, such as omalizumab and other biologic drugs. In addition, the article

examines possible future treatment options based on recent findings about pathogenic mechanisms, and considers the treatment of antihistamine-unresponsive urticaria in special conditions such as children and pregnancy/lactation. The evidence supporting the use of several of the discussed drugs is presently limited and thus insufficient to recommend their routine use; as a consequence, such compounds should be considered only in specific cases and in adequate settings.

1 Introduction

Chronic urticaria (CU), a skin disorder characterized by the continuous or intermittent eruption of short-lived wheals, which can be associated with angioedema, for more than 6 weeks [1], may heavily impair the quality of life [2, 3]. Second-generation H₁-antihistamines, either at the licensed dosage or at higher than the licensed dosage, represent unquestionably the mainstay of CU treatment and are able to control the disease in the majority of patients. However, a significant proportion of patients with CU remain poorly controlled despite treatment with elevated doses of second-generation H₁-antihistamines. These subjects often represent a severe challenge for the clinician. This article critically reviews the available treatments for antihistamine-resistant patients with CU, providing some information about the quality of evidence and the strength of recommendation (Table 1) [4]. The rationale for the use of most immunomodulatory and anti-inflammatory drugs that are reviewed comes from the detection of histamine-releasing autoantibodies [5–7], as well as from the demonstration of an increase in inflammation and coagulation biomarkers [8–10]. These treatments have

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Table 1 Profiles of the most commonly used drugs for the treatment of chronic spontaneous urticaria

Drug	Efficacy	Safety	Quality of evidence	Cost	Strength of recommendation
Second-generation antihistamines (at licensed doses)	High	Very good	High	Low	Strong
Second-generation antihistamines [at high doses (up to 4×)]	High	Good	Moderate	Low	Weak
Oral corticosteroids (short course)	High	Moderate	Low	Low	Weak
Leukotriene receptor antagonists (as add-on therapy)	Low	Good	Low	Moderate	Weak
Ciclosporin	High	Moderate	Moderate	High	Weak
Omalizumab	High	Good	High	Very high	Weak

Quality of evidence and strength of recommendation for use of intervention are based on the GRADE system [4] (updated to September, 2013)

been reviewed and included, with minimal differences, in the position papers endorsed by several international as well as national scientific societies, including the European Academy of Allergy and Clinical Immunology (EAACI), the American Academy of Allergy, Asthma & Immunology (AAAAI), and the World Allergy Organization (WAO) [11–15].

2 Corticosteroids

It is generally accepted that oral corticosteroids are able to control the disease in most CU patients who do not respond to antihistamines. However, surprisingly enough, no controlled study has been carried out so far to show their efficacy. In one recent, large, retrospective study, oral prednisone at a dose in the range of 0.3–0.5 mg/kg was able to induce a remission of the disease (followed by control with antihistamines at licensed doses) in about 50 % of cases [16]. In addition, the majority of the remaining patients responded to the treatment but relapsed when doses were tapered down, or after prednisone withdrawal. A second course of prednisone induced a persistent remission of the disease in about one third of the temporary responders. Prednisone effects were clinically evident as early as the day after the first 25-mg dose.

The main problem with systemic corticosteroids is the potentially severe adverse effects associated with long-term treatment (diabetes mellitus, hypertension, osteoporosis, gastrointestinal bleeding, and weight gain). Thus, oral corticosteroids should be used for short periods and at the minimal effective dose. Altogether, the policy of giving 25 mg of prednisone for 3–5 days along with gastrointestinal protection and then to taper it down seems a reasonable compromise between efficacy and avoidance of most adverse effects. However, there is the need for controlled studies to support the short-term use of oral corticosteroids.

3 Leukotriene Receptor Antagonists

The cysteinyl-leukotriene receptor antagonists montelukast and zafirlukast have been reported to be effective in patients with antihistamine-resistant CU both in anecdotal reports and placebo-controlled studies [17–23]. In most cases, they were used in combination with H₁-antihistamines as an add-on treatment, and seemed particularly useful in autoreactive patients (i.e., those showing a positive autologous serum skin test) and in those intolerant to aspirin or to food additives [19, 23]. The efficacy of zileuton, an inhibitor of leukotriene synthesis, in CU has also been reported [24].

The effectiveness of leukotriene receptor antagonists in CU, particularly when they are used as a single treatment, has not been confirmed by other studies [25]. Altogether, there is limited evidence of effectiveness of these drugs; furthermore, some criticism has been raised regarding the cost of their combination with high-dose H₁-antihistamines. Nevertheless, in view of their excellent safety profile, antileukotrienes might be tried in antihistamine-resistant patients before considering other, more engaging, drug options.

4 Anti-Inflammatory Drugs

Under this heading there are different drugs whose evidence of efficacy in CU is often limited but that are inexpensive and relatively safe. These drugs might represent an alternative to more expensive and/or toxic agents; however, they are not recommended by all the current guidelines on the treatment of CU.

4.1 Dapsone

A case report [26] and an open uncontrolled study in 11 patients [27] showed the effectiveness of dapsone at the

dosage of 25–50 mg/day in different sorts of chronic urticaria/angioedema, including spontaneous CU, although the addition of dapsone to desloratadine did not reduce urticaria activity scores compared with desloratadine alone (but was associated with a higher rate of complete remissions) in a randomized open study [28]. Dapsone is generally well tolerated, but may rarely cause dose-related anemia, along with peripheral neuropathy, skin rash, gastrointestinal complaints, hepatotoxicity, methemoglobinemia, blood dyscrasias, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Further, it is contraindicated in G6PD-deficient subjects because of the risk of severe hemolysis. Altogether, its use requires a careful follow-up of the patient [15].

4.2 Sulfasalazine

Some case reports and one single retrospective observational study suggest the effectiveness of this drug in CU [29–32]. Up to 2 g/day are needed for an effective treatment and response occurs within 1 month of therapy. The main adverse effects include nausea, vomiting, dyspepsia, anorexia, and headache, and less frequently hematologic abnormalities, proteinuria, and hepatotoxicity [15].

4.3 Hydroxychloroquine

A randomized, double-blind, placebo-controlled study showed a significant improvement in quality-of-life scores in patients with CU treated with hydroxychloroquine, although urticaria activity scores changed only marginally [33]. Although very rare, hydroxychloroquine bears the risk of retinopathy; such an adverse effect is associated with a prolonged use (>5 years) of the drug.

5 Immunosuppressive Drugs

5.1 Calcineurin Inhibitors

Several case reports and case series [34–36] as well as controlled trials [37–40] have shown for more than 20 years the effectiveness of ciclosporin in antihistamine-resistant CU. It is generally agreed that effective doses are in the range of 3–5 mg/kg/day, and that the treatment should last for approximately 3–6 months. During the treatment period, blood pressure, kidney function, and liver function should be assessed regularly. Once the drug course has been completed, remission may last up to 9 months in about 50 % of patients, while other patients show a decreased number of flare-ups and a restored response to antihistamine treatment [38]. However, some patients tend to relapse after drug discontinuation; long-

term maintenance therapy with low-dose ciclosporin (1.5–2.0 mg/kg/day) for some years (up to 5–7) has been suggested in these cases [41].

Another calcineurin inhibitor, tacrolimus, was found to be effective in patients with antihistamine-resistant CU in an open prospective study [42].

5.2 Other Immunosuppressive Agents

A number of other immunosuppressive agents have been used to treat severe, unremitting, antihistamine-resistant CU [43]. However, the quality of supporting evidence on the use of these drugs is low because only case reports and open uncontrolled studies are available. Methotrexate at a weekly mean dosage of 15 mg seems effective and safe in most CU patients who are not responsive to conventional therapy [44, 45].

Intravenous and oral cyclophosphamide has shown good efficacy in patients with autoreactive CU [46, 47].

Similarly, azathioprine [48] was effective in patients with antihistamine-resistant CU with a positive autologous serum skin test.

Mycophenolate mofetil, an inhibitor of purine biosynthesis, has recently been reported as a possible therapeutic option for CU patients who do not respond to antihistamines and/or corticosteroids [49, 50].

Similarly, mizoribine, another inhibitor of purine biosynthesis, has been reported to be effective in CU [51].

6 Biologicals

6.1 Omalizumab

The recombinant humanized monoclonal IgG antibody omalizumab binds free IgE, downregulates mast cell function, and induces eosinophil apoptosis [52–54]. It has been employed for several years as an add-on therapy for severe allergic asthma. More recently, the drug has emerged as an effective treatment for different subsets of antihistamine-unresponsive CU/angioedema of both autoimmune/autoreactive and non-autoimmune/autoreactive origin, as shown by a number of case reports, case series, and lately by multi-center double-blind, placebo-controlled studies [55–65]. Initially, case reports and case series suggested that omalizumab improved wheals and pruritus in patients with CU uncontrolled by H₁ antihistamines. Later, a phase II study including 90 patients with CU confirmed and extended these findings [60]. A subgroup of patients with CU with IgE antibodies against thyroperoxidase who were refractory to conventional treatment also showed a good response to omalizumab [59]. Moreover, a randomized, double-blind, placebo-controlled trial

involving 323 patients [64] demonstrated the efficacy and tolerability of subcutaneous omalizumab at the dose of 150 or 300 mg in patients aged 12–75 years with CU. Over 12 weeks (dosing at 4-week intervals), omalizumab efficacy was found to be dose dependent, with the greatest effects at 300 mg. Finally, in a recent phase III study, 336 patients with H₁-antihistamine-resistant CU were randomized to receive six subcutaneous injections at 4-week intervals of either 300 mg of omalizumab or placebo, followed by a 16-week observation period. Omalizumab was well tolerated and reduced the signs and symptoms of CU; however, after drug discontinuation, symptoms gradually recurred over a period of about 10 weeks [65]. Another limitation to the use of this drug is the high cost.

6.2 Intravenous Immunoglobulin

Intravenous immunoglobulin has been suggested as a possible therapeutic option in patients with chronic, unremitting urticaria with a positive autologous serum skin test and basophil histamine release assay who do not respond to other therapies by some case reports and by an open-label trial [66–69]. In the largest study, nine out of ten patients responded at a dose of 0.4 g/kg/day for 5 consecutive days and in three cases prolonged remission after a 3-year follow-up was observed. However, other studies did not confirm such favorable results [70]. Intravenous immunoglobulin is relatively safe, as adverse reactions such as anaphylactoid reactions, aseptic meningitis, and renal failure are only rarely reported [15], but its high cost is a limitation to its use.

6.3 Rituximab

The chimeric monoclonal antibody rituximab is specific for the protein CD20, which is primarily found on the surface of B cells. It destroys B cells, and thus reduces the production of antibodies including autoantibodies. Rituximab was effective in two CU patients resistant to H₁-antihistamines [71, 72], but was ineffective in a third case [73].

7 Anticoagulants

Recent studies showed that CU is frequently characterized by an increase of plasmatic markers of thrombin generation and fibrinolysis during severe exacerbations of the disease [74–76], possibly as a consequence of tissue factor expression by activated eosinophils [74, 77]. The activation of coagulation and fibrinolysis decreases till complete normalization during remission [75, 78]. Whether the activation of coagulation/fibrinolysis plays a pivotal pathogenic role in the disease or acts simply as an amplification system

has still to be defined. However, the fact that such an activation parallels the activity of CU may provide the rationale for an anticoagulant and antifibrinolytic therapy in patients with severe CU. The effectiveness of anticoagulant therapy in some patients with refractory CU was observed more than a decade ago [79] by the use of oral anticoagulants and more recently by the use of heparin [80, 81].

An interesting, indirect confirmation to the possible role of the coagulation pathway in the pathogenesis of CU comes from recent studies reporting the efficacy of serine protease inhibitors nafamostat mesilate and camostat mesilate in refractory CU [82]. Such drugs inhibit different proteases, including tryptase, kallikrein, complement, factor XII, and plasmin, and show an anticoagulant effect similar to that of heparin [83].

8 Other Treatments

Plasmapheresis has been suggested as a possible treatment in patients with severe, unremitting, and refractory CU [84]; however, such an approach is not easily available and cannot be recommended for routine use.

In a randomized, controlled, multicenter study, miltefosine, a lipid raft modulator, has been shown to reduce urticaria symptoms in CU patients who do not respond to standard-dosed H₁-antihistamines [85].

9 Special Conditions

9.1 Childhood

Second-generation H₁-antihistamines are the treatment of choice in children with CU and generally are highly effective; however, a few cases are not controlled by H₁-antihistamines at licensed doses. An increase of drug dosage can be tried, but controlled studies of efficacy and long-term safety of high doses of H₁-antihistamines in children are lacking. A short course of prednisone may be administered to control symptoms, similarly to adult patients [86]. Ciclosporin has been found to be safe and highly effective in seven pediatric patients with H₁-antihistamine-resistant CU [87]; however, controlled studies are lacking. There are no pediatric controlled studies on the use of leukotriene receptor antagonists, H₂-antihistamines, or omalizumab for the treatment of CU.

9.2 Pregnancy and Lactation

In pregnant women, CU may improve or, in a few cases, may worsen. In general, medications should be avoided during pregnancy; however, if a pharmacological treatment

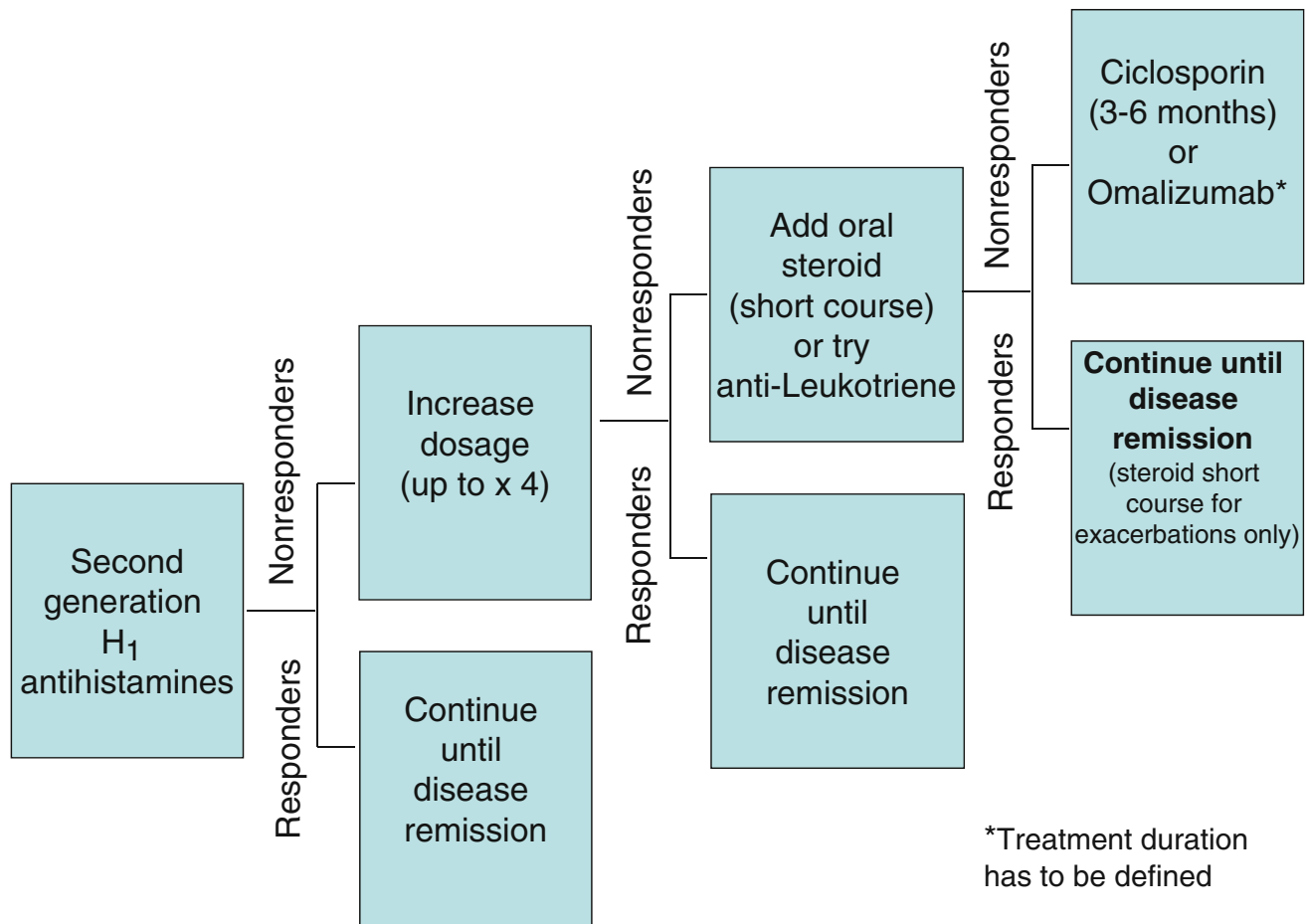


Fig. 1 Therapeutic algorithm in chronic spontaneous urticaria

is needed to control symptoms, H₁-antihistamines represent the drugs of choice [15]. There are no oral antihistamines with a category A listing for pregnancy. Categories are based on the results of animal studies, human data, and whether the use of the drug has a positive risk–benefit ratio in pregnancy. Category ‘B’ drugs possess reassuring animal data, but there are no controlled clinical human trials. Chlorpheniramine, loratadine, cetirizine, and levocetirizine belong to category B according to the US FDA. H₁-antihistamines should only be used during lactation when the benefit outweighs the potential harm to the infant because variable amounts of antihistamines can be detected in breast milk. A short course of corticosteroids can be administered during pregnancy in the case of severe exacerbations of urticaria. Although risks are very low, three potential areas of concern have been raised: congenital malformations (primarily cleft palate in the first trimester), neonatal adrenal insufficiency, and low birth weight. Low levels of prednisone and prednisolone can be measured in breast milk; however, their use appears to be safe during breast-feeding. There are no controlled studies on the use of omalizumab in pregnant women with CU and

there is limited clinical experience with the use of this medication during pregnancy in asthmatic women. The FDA has classified omalizumab as category B. No experience is available regarding the use of ciclosporin in pregnant women with CU, and presently cannot be recommended in H₁-antihistamine-resistant CU. However, ciclosporin is used in transplanted patients who require immunosuppression during pregnancy, as well as tacrolimus and azathioprine. In contrast, cyclophosphamide, methotrexate, and mycophenolate mofetil are teratogenic drugs and must be avoided during pregnancy [15].

10 Chronic Urticaria Treatment in Clinical Practice

It is generally accepted that CU patients should undergo a stepwise treatment (Fig. 1), considering that in most cases stepping-up implies an increase in both direct and indirect costs and in the risk of adverse effects. Although sometimes heavily disturbing and long lasting, CU is not a life-threatening disease and does not pose a risk for organ failure; thus, the objective of the treatment should be to

control the disease as best as possible with the least adverse effects. In many cases of severe disease, a step-down will be possible following a period of treatment with anti-inflammatory/immunosuppressive drugs.

Once ascertained that the patient does not respond satisfactorily to second-generation antihistamines (even at higher than licensed doses) and to leukotriene receptor antagonists as an add-on therapy, we suggest to try one or two short courses of oral corticosteroids. If the disease relapses soon after the oral corticosteroid is tapered down and requires a continuous administration to be controlled, the next option should be ciclosporin. In non-responders to H₁-antihistamines, even at high doses, omalizumab can be considered, although its high costs and limited availability represent a problem in most settings. The evidence supporting the use of the other drugs mentioned before (immunosuppressive, anti-inflammatory, and anticoagulant drugs, IVIG) is presently not sufficient to recommend their routine use; such compounds should be considered only in specific cases and in adequate settings.

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