

## Treatment of Chronic Urticaria

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**SUMMARY** Urticaria is a disorder characterized by rapid onset of localized swelling of the skin or mucosa, called wheals or urtica. According to frequency and duration, urticaria can be divided into acute and chronic type. Chronic urticaria is any type of urticaria occurring every day or twice *per* week, lasting longer than 6 weeks. Chronic urticaria is a common disorder and estimated prevalence is 1% of the population. Also, it is not rare in childhood.

The pathogenesis of chronic urticaria has not yet been completely understood. Chronic urticaria is a heterogeneous group of disorders, and according to the etiology and cause, several groups of chronic urticaria are distinguished, i.e. autoimmune, pseudoallergic, infection-related, physical urticaria, vasculitis urticaria and idiopathic urticaria. Treatment and management of chronic urticaria can be non-pharmacological and pharmacological, and sometimes it is not possible to control the disease with antihistamines only, which are considered to be the mainstay of treatment. In severe cases of chronic urticaria, especially if autoimmunity has been proven, several authors describe different modules of immunomodulation: cyclosporine, cyclophosphamide, mycophenolate-mofetil, omalizumab, plasmapheresis, systemic corticosteroids, and immunoglobulin therapy. This article primarily addresses the treatment of chronic idiopathic and autoimmune urticaria.

**KEY WORDS:** chronic urticaria, H1 antagonist, corticosteroids, autoimmune urticaria, chronic idiopathic urticaria, immunomodulators

### INTRODUCTION

Urticaria is presented with short-lived swelling of the skin and mucosa due to transient leakage of plasma from small blood vessels into the surrounding tissue (1). Wheals or hives are superficial swelling of the dermis and are itchy. Any pattern of recurrent urticaria occurring twice weekly for

6 weeks is called chronic urticaria (1). There are no reliable data on the prevalence of chronic urticaria, but it is estimated at 1% (2). In some cases, there is involvement of deep dermis and subcutaneous tissue and it is presented as angioedema and can affect both the skin and mucosa (3,4).

Angioedema may be rather painful than itchy, and can coexist with wheals, however, wheals and angioedema can appear alone (1). The diagnosis of chronic urticaria is made on the basis of clinical appearance, detailed history data on the onset and duration of individual wheals, and also exclusion of some infective agents and systemic diseases such as thyroid gland disease and some other autoimmune disorders. Chronic urticaria is a heterogeneous disorder that can be divided into autoimmune, pseudoallergic, infection-related, physical, vasculitis and idiopathic urticaria (1). This article addresses autoimmune and idiopathic chronic urticaria, which pose a therapeutic problem.

The pathogenesis of chronic urticaria is still poorly understood. The term "chronic urticaria" makes no assumption about its cause, but it is sometimes used closely to term "chronic idiopathic urticaria" (CIU). It is not justified because a large proportion of CIU can be ascribed to autoimmunity (1). About 50% of cases remain unexplained after evaluation for autoimmunity (1). CIU can be a very disabling condition and it can severely interfere with daily activities, quality of life and sleep. CIU is a common skin condition that affects 0.1%-0.3% of the population in the USA and Europe and accounts for nearly 75% of all chronic urticaria cases (5).

In pediatric population, causative agents are identified in about 20% of cases (3). About 5%-10% are caused by physical factors; other triggers are infections (mostly viral), foods, additives, aeroallergens and drugs (3). CIU is defined by exclusion of other possible causative agents. About one third of children with chronic urticaria have circulation autoantibody against high-affinity IgE receptor or against IgE. It is not known why these antibodies are produced or how they alter the course of the disease.

Besides histamine, other mediators such as prostaglandins, leukotriens and kinins are also involved, and it is often quite difficult to treat urticaria with antihistamines alone (4). In 2006, a review article on EEACI/GA<sup>2</sup>LEN/EDF guideline for definition, classification and diagnosis of urticaria was published by Zuberbier *et al.* (6). According to this guideline, the classification of urticaria is made on the basis of its duration, frequency and causes. The diagnosis is based on detailed patient personal and family history. The authors recommend the following questions to ask: 1) time at onset of disease, 2) frequency and duration of wheals, 3) diurnal variation, 4) shape, size and distribution of wheals, 5) associated angioedema, 6) associated symptoms of lesion, 7) family history regard-

ing urticaria and atopy, 8) previous or current allergies, infections, internal diseases, 9) induction by physical agents or exercise, 10) use of drugs, 11) food, 12) smoking habits, 13) type of work, 14) hobbies, 15) occurrence on weekends, holidays and foreign travel, 16) surgical implants, 17) reaction to insects, 18) connection to menstrual cycle, 19) stress, and 20) quality of life. Thorough history should be followed by physical examination and testing for dermographism (2,6).

Different types of urticaria require different diagnostic work-up algorithms. Once the pseudoallergic reactions and underlying diseases have been excluded, the likelihood of finding the cause is very low. It is necessary to obtain very detailed history data on the medications taken *per need*, which are usually forgotten by the patient him/herself, e.g., for headache, since pseudoallergic reactions to nonsteroidal antiinflammatory drugs (NSAID) are not rare. When analyzing food as the possible cause, the main problem is identification of additives and preservatives, which should be excluded from dietary habits because certain foods can cause pseudoallergic reactions, e.g., reaction to tartrazine can be one of the manifestations of hypersensitivity to acetylsalicylic acid. Urticaria and angioedema can appear as a symptom of systemic disease (collagenopathies, malignancies, hemolytic diseases, endocrinopathies, celiac disease), or can be congenital (hereditary angioedema) (3). There is an increasing incidence of thyroid disease in patients with urticaria (3). IgE independent reactions are common in adult patients with chronic urticaria.

Almost every malignancy has been reported to be associated with urticaria. It is recommended to exclude malignancies, especially in elderly patients or in patients with symptoms of losing weight and other nonspecific symptoms. A variety of hematopoietic malignancies and malignancies of gastrointestinal tract are probably most important to exclude. It is recommended to perform fecal occult blood test, Pap smear, screening for prostate and pelvic examination. From our experience, it is reasonable to start with serum markers for malignancies.

Some reports show connection with *Helicobacter (H.) pylori* infections; screening revealed a higher incidence of asymptomatic *H. pylori* infections in a group of patients with chronic urticaria. Also, stool can be tested for *Candida albicans* and other parasitic infestations. Anyhow, a very small proportion of chronic urticaria cases are infection-related (1).

The only test for autoantibodies against IgE receptor available is autologous serum skin test, which shows the presence of serum histamine releasing factors of any type, not just antibodies (6). Another useful method is evaluation of histamine release from basophils, however, it is not performed routinely (6). Besides autoimmune pathogenesis mediated by functionally active autoantibodies to the high affinity IgE receptor or to IgE, which are able to induce histamine release from basophils and mast cells and are found in only 50% of patients with chronic urticaria, a few more pathomechanisms must obviously be involved.

It has been recently published that an additional pathogenetic mechanism may be involved; there is activation of coagulation cascade and production of thrombin, a serine protease involved in edema formation due to the increase in vascular permeability, mast cell activation and degranulation, and production of anaphylatoxin C5a (7,8).

It is necessary to identify the trigger; trigger removal is the only causal treatment and also identification of contributing agents, for example, use of NSAIDs causes worsening of chronic urticaria.

It is also important to note that extensive laboratory tests are not necessary in all cases; it depends on history data. Chronic urticaria can persist for many years, but resolves spontaneously in 30%-55% of patients (4).

## MANAGEMENT OF CHRONIC URTICARIA

The EAACI/GA<sup>2</sup>LEN/EDF guideline for the management of urticaria is a consensus reached during panel discussion at the Second International Consensus Meeting on Urticaria, Urticaria 2004, a joint initiative of the EAACI Dermatology Section and GA<sup>2</sup>LEN (9). According to this guideline, management is divided into three basic approaches. First approach is avoidance, elimination or treatment of eliciting stimulus or cause. This is the best way since identification of the cause allows for successful treatment; however, it may not be possible in all cases. It includes elimination of medicaments, physical stimuli, eradication of infectious agents and treatment of inflammatory processes, and also removal of FcεRI autoantibodies. It is applicable in patients with some IgE-mediated or physical urticaria. Second approach is inhibition of mast cell mediator release and nowadays the most commonly used drugs inhibiting mast cell release are corticosteroids. Other drugs with inhibiting activity on mast cells are, for example,

cyclosporin A and PUVA therapy. Third approach is therapy to target organ, e.g., antihistamines.

Many pharmacological and non-pharmacological treatments are available. None of them is universal and treatment should be tailored individually. The mainstay of treatment for all types of urticaria are antihistamine agents and they are first-line therapy (1). Providing understandable and useful information is necessary, e.g., already mentioned avoidance of NSAIDs and use of acetaminophen when analgesics or antipyretics are required, because NSAIDs aggravate the symptoms of chronic urticaria (12). It is also recommended to avoid codeine and other opiates due to enhanced skin test for codeine in patients with chronic urticaria. Aggravation of chronic urticaria is usually seen during viral infection and it is often difficult to differentiate whether aggravation is due to the reaction to virus or due to the medication taken. It is also recommended to avoid dietary pseudoallergens such as food additives and colors, preservatives and natural salicylates (1,2,12-14).

## ANTIHISTAMINE AGENTS

Antihistamines are considered as first-line therapy (15). Antihistamines reduce itch, whealing, or both (1,16). Antihistamines not only relieve itching, but they also reduce the number, size and duration of urticarial lesions (16). Histamine is a mediator of itch, but also few other mediators are involved such as mast cell tryptase and substance P (17).

Antihistamines are traditionally divided into groups. First generation of antihistamines is represented by promethazine, hydroxyzine, chlorpheniramine, deschlorpheniramine, ketotifen and cyproheptadine, and these drugs have sedative effect. Cetirizine, loratadine, mizolastine, ebastine and terfenadine are antihistamines of second generation. The new generation of antihistamines is represented by fexofenadine, desloratadine and levocetirizine.

All patients should be offered at least 2 non-sedating or minimally sedating agents. Antihistamines should be taken daily, not *per need*. Histamine H1 receptor antagonists are the only drugs licensed for use in urticaria (1,18,19). Newer generation antihistamines are effective and safe at higher doses, although higher rates of sedation have been demonstrated with higher doses of some agents, e.g., cetirizine (18,19).

Good therapeutic response has been reported in 55% of patients with CIU (20). In 94% of patients antihistamines are effective in itch relief, so

the first therapeutic choice should always be an antihistamine agent (21).

First generation antihistamines are the sedating ones. Although newer antihistamines are considered as non-sedating when administered in higher doses, some sedation and drowsiness can be experienced, especially in first months of therapy, slightly more when levocetirizine is used when compared to desloratadine (22,23). Sedation may reduce discomfort, especially at bed time, but sedation is potentially dangerous during the day since it impairs driving performance and decreases work capability (1).

Some authors suggest the use of non-sedating second generation antihistamines in the morning and the sedating ones in the evening (24). Sedating antihistamines have more adverse effects and should be reserved for patients who do not respond to the low-sedating group of antihistamines (1). Second generation antihistamines do not induce sedation, with the exception of cetirizine (19,25).

The risk of ventricular arrhythmias associated with non-sedating antihistamine drugs is very low. According to the authors, the use of non-sedating antihistamine drugs increases the risk of ventricular arrhythmia by factor four in the general population, requiring 5300 person/year of use for one case to occur (26, 27).

According to recent literature data, it is better to treat chronic urticaria daily, by continuing therapy, than to treat it only when the symptoms return (28).

Although H1 receptor-mediated reactions are responsible for vasoactivity, vasopermeability and itching, it is clinically observed that the addition of H2 receptor antihistamine to H1 receptor antihistamine may provide better effect. According to literature data, H2 receptor blocker have potential effects with H1 blocker in suppressing histamine-induced wheal (29).

Second-generation histamine H1 receptor antagonists have been developed to provide efficacious treatment of allergic rhinitis and CIU, combined with decreasing adverse effects which were associated with first generation agents. Second generation antihistamines are highly selective for H-1 receptor. They have shown limited effects on the central nervous system, with almost no significant drug-drug interactions noted in clinical studies. No major cytochrome P450 inhibition has been reported with desloratadine, fexofenadine and levocetirizine, and the bioavailability of deslo-

ratadine is minimally affected by drugs interfering with transporter molecules. Of second generation antihistamines, desloratadine has the greatest binding affinity for H-1 receptor (30).

**Fexofenadine (Telfast®)** is a non-sedating antihistamine, which also shows an anti-inflammatory action (31). Fexofenadine is an active metabolite of terfenadine. It does not affect driving or psychomotor performance and has been shown to improve quality of life in patients with seasonal allergic rhinitis and chronic urticaria (33). It has a high margin of safety and is also well tolerated in patients with renal or hepatic impairment, in children and the elderly. No clinically significant drug interactions have been identified. It is not associated with cardiotoxicity (33,34). There is a single case report with QT lengthening and life threatening arrhythmia in a patient with pre-existing heart disease (35). Unlike some other antihistamines such as loratidine or cetirizine, fexofenadine is truly non-sedating and shows no dose-related increase in sedation, even at high doses. It is formulated as the hydrochloride salt. The recommended dose of fexofenadine HCl is 120 mg daily for seasonal allergic rhinitis (either as 120 mg once daily or 60 mg twice daily) and 180 mg once daily for CIU (33,36).

According to data from a recent study, a significant decrease was demonstrated in the expression of ELAM-1, VCAM-1 and tryptase, and these preliminary data show a trend towards a decrease in the expression of these molecules after treatment, suggesting an anti-inflammatory activity of fexofenadine (31). The most common adverse event is headache (34). No effect on psychomotor abilities or cardiac arrhythmia were observed.

A new oral suspension formulation of fexofenadine has been developed for the indication of seasonal allergic rhinitis symptoms in children aged 2-11 years and for uncomplicated skin manifestations of CIU in children aged 6 months to 11 years. Clinical studies have shown the oral suspension to have both bioequivalence with the 30-mg tablet formulation and a favorable safety and tolerability profile (37).

When compared to montelukast, fexofenadine suppressed the allergen-induced wheal-and-flare response to a significantly greater extent, and had a significantly faster onset of action (38). When compared to desloratadine, fexofenadine has a faster onset of flare suppression than desloratadine (1 hour vs. 5 hours) and an as rapid onset of wheal suppression. Fexofenadine HCl, 180 mg,



was superior to desloratadine, 5 mg, in histamine-induced wheal-and-flare suppression, suggesting an increased *in vivo* H1-receptor antagonist potency of fexofenadine *versus* desloratadine (39).

**Desloratadine** (Clarinet<sup>®</sup>, Neoclaritin<sup>®</sup>, Aeri-us<sup>®</sup>, Azomyr<sup>®</sup>, Opulis<sup>®</sup>) is a rapid-acting, once-daily, non-sedating selective H1-receptor antagonist/inverse receptor agonist with proven clinical efficacy in patients with CIU (40). It has 10- to 20-fold *in vivo* H1 receptor-binding affinity of loratadine, and 52- to 194-fold H1 receptor-binding affinity of cetirizine, ebastine, loratadine and fexofenadine. It has linear pharmacokinetics after oral administration. There are no drug and food interactions, and it does not impair the psychomotor ability (40-42). It is also important to note its anti-inflammatory effects independent of H1-receptor antagonism. According to the authors, once-daily desloratadine 5 mg is well tolerated and superior to placebo in reducing pruritus and wheals associated with CIU. It provides rapid and sustained relief of CIU symptoms as early as after the first dose and maintains this effect until the end of 6-week treatment period (43). Desloratadine is an active metabolite of loratadine, and is safe and well tolerated. The most common adverse event is headache, with no relevant changes recorded in ECG and laboratory tests (44). In 2004, the ARIA/EAACI report appeared assessing the efficacy, safety and pharmacology of desloratadine (45). This document outlined the need for determining the clinical efficacy of antihistamines in terms of disease and symptom control rather than in simulated models. It is also noted that there is no third generation of antihistamines. Based on this systematic review, the authors conclude that the efficacy, safety and pharmacology meet the ARIA/EAACI criteria for antihistamines (45). Desloratadine has an inhibitory effect on IL-3, IL-6, IL-8, TNF- $\alpha$  and GM-CSF release from mast cells and basophils in humans (46). Results of *in vitro* and *in vivo* studies have suggested that desloratadine has anti-allergic effects that are unrelated to its ability to antagonize the effects of histamine. Desloratadine inhibits the expression of cell adhesion molecules, inhibits the generation and release of inflammatory mediators and cytokines, and attenuates eosinophil chemotaxis, adhesion and superoxide generation (47,48).

The safety profile of desloratadine is excellent (48,49). So far, no effect on QRS and QTc intervals has been observed and it does not cause arrhythmias. Desloratadine is not associated with any significant changes in gastrointestinal

function. In clinical studies, oral desloratadine is rapidly absorbed and bioavailability is not affected by ingestion of food or grapefruit juice. The half-life of desloratadine in humans is 27 h; the linear kinetic profile is unaltered by race or sex. Desloratadine is not a substrate for P-glycoprotein or organic anion transport polypeptide and the drug does not appear to be metabolized to a significant extent by the cytochrome P450 CYP3A4 pathway. It therefore may be safely administered with ketoconazole, erythromycin, fluoxetine, or azithromycin (48).

Some recent findings suggest the involvement of oxidative stress in the pathogenesis of CIU. There are some preliminary results that desloratadine exerts antioxidant effects *in vivo* (51). It has been shown in multiple studies to be safe and effective in relieving the symptoms of allergic rhinitis and CIU in adults and adolescents, but also in children aged 2-11 years with allergic rhinitis or CIU (52). When compared to levocetirizine, levocetirizine 5 mg was significantly more efficacious than desloratadine 5 mg in the treatment of CIU symptoms (53,54). Desloratadine can be combined with dapson in the treatment of chronic urticaria (55). One group of authors assessed the efficacy and safety of desloratadine combined with dipyrindamole in the treatment of chronic urticaria and found significant difference when compared with a group treated with desloratadine only (56).

Recently, antileukotriene receptors have been used in patients with CIU, either administered as monotherapy or combined with H1-receptor antagonists. According to the authors, patients were treated with 5 mg of desloratadine once daily, 10 mg of montelukast once daily, 5 mg of desloratadine in the morning plus montelukast in the evening, and compared with placebo. According to study results, regular combined therapy with desloratadine plus montelukast did not seem to offer a substantial advantage with respect to desloratadine as monotherapy in patients affected by moderate CIU (57). Other authors found some benefit in the treatment of seasonal allergic rhinitis with the addition of antileukotriene antagonist to antihistamine therapy. This combination is believed to exert additional anti-inflammatory activity as provided by reduction of inflammatory infiltrate and cytokine levels. It is observed that cetirizine might exert more beneficial activity than desloratadine when added to montelukast (58).

**Levocetirizine (Xyzal<sup>®</sup>)** is an R-enantiomer of cetirizine dihydrochloride. Levocetirizine has high bioavailability, high affinity for and occupancy of H1 receptor (30). It has shown rapid onset of

action. Levocetirizine is safe and effective for the treatment of allergic rhinitis and CIU in adults and children with a minimal number of undesirable effects (59-63). Levocetirizine does not prolong the QT/QTc interval in healthy subjects, as demonstrated in thorough QT study (30,64). It undergoes minimal hepatic metabolism, and is largely eliminated by urine, therefore, dose reduction is recommended in patients with renal impairment (4). Levocetirizine has several anti-inflammatory effects (65). It is indicated for PAR and CIU. Some antihistamines are capable of reducing levels of adhesion molecules in patients with chronic urticaria. Levocetirizine 5 mg daily demonstrated a broad anti-inflammatory effect in patients with chronic urticaria. The significant decrease in serum levels of ELAM-1 and P-selectin might reflect the inhibitory activity on neutrophil rolling and extravasation towards inflamed skin (65,66). It has recently been published that levocetirizine modulates lymphocyte activation in patients with allergic rhinitis. Study data showed reduced percentage of eosinophils and three subpopulations of activated T lymphocytes, CD4+CD29+, CD4+CD212+ and CD4+CD54+. Levocetirizine treatment also correlated with a significant increase in the percentage of CD4+CD25+ T cells. The ability of levocetirizine to reduce percentage representation of cell phenotypes known to contribute to inflammatory tissue damage (eosinophils, CD4+CD29+, CD4+CD212+, and CD4+CD54+) and expand the percentage of CD4+CD25+, which may include protective immunoregulatory (Treg) cells, indicates that the drug has a pharmacological potential beyond the immediate effects of H1 histamine-receptor inhibition (67,68).

On comparison of levocetirizine 5 mg and desloratadine 5 mg, levocetirizine 5 mg was significantly more efficacious than desloratadine 5 mg in the treatment of CIU symptoms (53,54).

Recently, one case report appeared on fixed drug eruption to cetirizine with positive lesional patch tests to three piperazine derivatives. This is the first report of fixed drug eruption to cetirizine with positive patch testing for hydroxyzine, cetirizine and levocetirizine (69).

**Ebastine** is a second-generation antihistamine that is effective in the treatment of seasonal allergic rhinitis and PAR. It is available as regular tablet or as fast-solving tablet formulation which disintegrates in the mouth without drink, and also in combination with pseudoephedrine (70). According to the authors, ebastine in a dose of 10 mg once daily improved symptoms to a significantly greater

extent than placebo and to a similar extent as loratadine 10 mg and cetirizine 10 mg (both once daily), while ebastine 20 mg proved to be more effective than these two comparator antihistamines. In addition, ebastine was significantly more effective than placebo in relieving the symptoms of CIU. Ebastine provides efficacy throughout the 24-h dosing interval with once daily administration and clinical benefit is seen from the first day of treatment. Small studies have found beneficial effects of ebastine in patients with other disorders, including cold urticaria, dermographic urticaria, atopic asthma, mosquito bites and in combination with pseudoephedrine for common cold (70,71). Ebastine 20 mg/day is indicated in patients with moderate and severe allergic symptoms. No cardiovascular effects of ebastine are described, although there is a pharmacokinetic interaction when ketoconazole or macrolides are co-administered (71). Ebastine does not affect psychomotor performance (70,71). Furthermore, ebastine 5-10 mg and 2.5 mg appears to be efficient and can be used safely in children 6-11 and 2-5 years of age, respectively (71). There is no need for dose correction in elderly patients, or in patients with renal or mild to moderate hepatic impairment (71). Ebastine appears to be a safe, effective and well-tolerated second generation antihistamine in the treatment of allergic rhinitis and CIU (70,71). However, there is one case report published in 2007 about ebastine induced hepatotoxicity (72). Other authors report good safety profile of ebastine (73-75).

In 2007, a comparative study on desloratadine 5 mg vs. ebastine fast-dissolving tablet 20 mg investigated inhibition of cutaneous histamine reaction in healthy non-atopic adults. All adverse events were mild or moderate and most participants expressed preference of fast dissolving formulation (75).

**Rupatadine** (Rupafin<sup>®</sup>, Rinialer<sup>®</sup>, Rupax<sup>®</sup>, Alergoliber<sup>®</sup>) is a newer dual inhibitor of histamine H(1)- and PAF (platelet-activating-factor)-receptors. It has been shown to be an effective and well-tolerated treatment for allergic rhinitis and CIU for patients aged over 12 years (76). Used once daily in a dose 10 mg it has a fast onset of action with rapid symptom relief, and it also has an extended duration of clinical activity. According to the authors, rupatadine was shown to be at least as effective as drugs such as loratadine, cetirizine, desloratadine and ebastine in reducing allergic symptoms in adult/adolescent patients with seasonal, perennial or persistent allergic rhinitis

and chronic urticaria. So far, no adverse cardiovascular effects were observed in preclinical or extensive clinical testing, or negative significant effects on cognition or psychomotor performance (including a practical driving study) (76-78). There is no drug interaction with azithromycin, fluoxetine and lorazepam, but it should not be administered with known CYP3A4 inhibitors (78).

### **DOXEPINE**

Doxepine is a tricyclic antidepressant drug. In a dose of 25-75 mg/day it has been shown to be effective in the treatment of chronic urticaria, without significant adverse side effects. Doxepine has combined H1, H2 and muscarinic blocking activities, which may explain its clinical efficacy in the treatment of chronic urticaria (79). Treatment with doxepine is very useful when chronic urticaria is associated with depression or anxiety. The drug can be given in a dose of 25 mg orally twice daily or as a single dose of 25 mg at bedtime. It should not be co-administered with terfenadine or monoamine oxidase inhibitors (79,80). It has been shown to be more effective and less sedating than diphenhydramine, and as effective as mequitazine in the treatment of CIU (80). Due to sedation, it should be given at bedtime.

### **LEUKOTRIENE RECEPTOR ANTAGONISTS**

Cysteinyl leukotrienes (CysLTs) are potent proinflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway. They exert important pharmacological effects by interaction with at least two different receptors, CysLT1 and CysLT2 (1,81). By competitive binding to the CysLT1 receptor, leukotriene receptor antagonist drugs such as montelukast, zafirlukast and pranlukast block the effects of cysteinyl leukotrienes. Recently published studies and case reports have demonstrated beneficial effects of leukotriene receptor antagonist (LTRAs) on other diseases commonly associated with asthma, e.g., exercise induced asthma, rhinitis, chronic obstructive pulmonary disease, interstitial lung disease, chronic urticaria, atopic dermatitis, allergic fungal disease, nasal polyposis, and paranasal sinus disease (81). LTRAs are not licensed for urticaria. However, there are some reports and small studies about beneficial effects of this group of drugs in CIU management (82).

According to Wan, the combination of LTRAs and H1 receptor antagonist is promising for CIU

treatment and is reasonably well tolerated by patients. Results of this study showed the combination of H1- and H2-receptor antagonists to provide highest treatment efficacy by the measures used in this study (82). Still, results of conducted studies are mixed. Several authors describe beneficial effects, whereas others found no therapeutic impact of the addition of LTRAs. One study compared the treatment of CIU with desloratadine alone and with desloratadine plus montelukast. According to study data, the combination of desloratadine plus montelukast was found to improve the symptoms and patient quality of life significantly more than desloratadine alone, although it did not have a significant effect on the number of urticarial episodes (57,83,84). Another comparative study of desloratadine alone, montelukast alone and a combination of these two drugs demonstrated desloratadine to be highly effective for the treatment of patients affected by CIU. In addition, the regular combined therapy with desloratadine plus montelukast did not seem to offer any substantial advantage over desloratadine monotherapy in patients with moderate CIU (57). In 2006, a review article appeared on montelukast; results of the studies analyzed were mixed and controversial. So far, no clear conclusion can be made and large controlled trials are lacking. However, it seems that LTRAs may prevent severe urticaria/angioedema exacerbations that follow the use of NSAIDs in some patients with chronic urticaria (86-88).

### **ORAL CORTICOSTEROIDS**

The most frequently used drugs inhibiting mast cell mediator release are corticosteroids. In general, corticosteroids should be avoided in long term treatment because of serious adverse events, while in acute urticaria short-term usage can be very helpful in order to reach fast symptom control. A short tapering course of corticosteroids may be useful in antihistamine resistant CIU, when rapid control is needed. Different schemes and dosages have been suggested in the literature, but it is common to start with prednisolone 40 mg/day, reduced by 5 mg every 5 days (1,4,89-91). It is usually recommended to continue with antihistamine therapy during this short course of antihistamines. Long term therapy should be avoided due to serious adverse events such as diabetes mellitus, hypertension, Cushing syndrome, osteoporosis, and others.

### **PLASMAPHERESIS**

A group of patients with chronic idiopathic urticaria have circulating functional autoantibodies

against the high affinity IgE receptor, or in some cases IgE antibodies. Whether autoantibodies cause chronic urticaria remains unknown, but intradermal injection of anti-FcεR1 IgG in healthy volunteers has been shown to cause urticarial reaction. So, there is a concept of chronic urticaria as a disease caused by autoantibodies activating the normal function of mast cells. Autologous serum skin test has proved to be a useful screening test for autoimmune urticaria. Identification of patients with autoimmune urticaria is important because immunotherapy can be necessary and useful, using cyclosporine, intravenous immunoglobulin, or even plasmapheresis in severe cases of therapy-resistant chronic urticaria (92). In 1992, in *Lancet*, a group of authors described plasmapheresis in the treatment of severe, unremitting chronic urticaria (93). In 2008, a group of authors published a case report of double-filtration plasmapheresis for resolution of refractory chronic urticaria. Double-filtration plasmapheresis removes medium to large molecular substances such as IgG and IgE from circulation and therefore can be an effective treatment option (94). Plasmapheresis is described by several authors as an alternative option for severe chronic urticaria unresponsive to other treatments, but it is not very often done (95).

### INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulins (IVIG) are used in patients with severe disease unresponsive to conventional treatment. As mentioned above, autoimmune pathogenic mechanism is implicated in about one-third of patients with chronic urticaria and involves circulating functional autoantibodies to either the high affinity IgE receptor (IgG1/IgG3 anti-FcεR1) or to IgE, with histamine releasing activity. A group of authors has described 29 patients with the diagnosis of autoimmune chronic urticaria treated with IVIG. They used low dose of IVIG treatment every 4 weeks (0.15 g/kg) for a minimum of 6 months and a maximum of 51 months. Twenty-six patients had improvement of symptoms and the need for oral antihistamine medication was decreased. Nineteen of 26 patients achieved complete remission of symptoms; 20 patients remained without symptoms for 12 months of active treatment; and six patients reported only mild complaints. The authors conclude that IVIG is an effective therapeutic option in patients suffering from severe chronic urticaria refractory to conventional treatment, in which autoimmune mechanism is involved. The efficacy persists for at least 12 months of treatment. However, the number of in-

fusions needed to achieve clinical control greatly varied among patients (96). In another study, ten patients with positive circulating anti-FcεR1 or anti-IgE antibodies were given IVIG 2 g/kg for 5 days and this therapy was efficient in nine patients and induced prolonged remission in three patients (97). One case report describes good result with low dose (0.2 g/kg) over one day. However, the authors point out that the results can last shortly (98).

### SULFASALAZINE

Sulfasalazine 500-4000 mg/day for the treatment of CIU has been reported in several articles. In 2006, a report appeared on 19 patients with antihistamine-unresponsive CIU treated with sulfasalazine between 2002 and 2005 (99); 74% of patients experienced significant improvement, 21% reported minimal improvement but were not satisfied with their symptom relief, and 5% reported worsening of symptoms. All patients that required systemic steroids for symptom control were able to reduce or discontinue steroid use during sulfasalazine therapy. Adverse effects were reported in 37% patients and included nausea, headache, mild or transient leukopenia, and elevation of transaminases, and were thought to be caused by sulfasalazine. Sulfasalazine can be used in patients with CIU that do not respond to antihistamines; it is a steroid sparing drug (4,99,100). There also are several case reports on successful sulfasalazine treatment of severe CIU associated with pressure urticaria and angioedema (101,102).

### METHOTREXATE

Two CIU patients successfully treated with methotrexate were described in 2001 (103). Seven patients with CIU treated with methotrexate 2.5 mg every 12 hours, two days a week for a 6-week period were reported in 2004 (104). Statistically significant improvement was observed in itching, presence of wheals and sleep quality. There was no statistical difference in the extension of lesions and presence of angioedema. Adverse effects were not significant. There are only several case reports, but the efficacy of methotrexate has not been proven in large controlled studies. There are few literature reports on pulmonary edema, sometimes even fatal, caused by methotrexate in low doses, and on pancytopenia that was observed with higher dose (106-108). The most important risk factor for methotrexate toxicity is impaired renal function. Pancytopenia can occur at any time during therapy with methotrexate.



### MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) has been registered for prophylaxis of solid organ allograft rejection. MMF is now increasingly used for indications outside solid organ allograft rejection, often with limited supporting efficacy data. First line of treatment of patients with chronic urticaria are oral antihistamines and around 50% of patients respond well to antihistamines; others need a more aggressive approach, immunosuppressive therapy such as oral corticosteroids or cyclosporine. MMF may be a valuable and safe treatment for patients with chronic urticaria that do not respond to antihistamines and/or corticosteroids, and that require aggressive treatment. In 2006, nine patients were reported that received 1000 mg twice daily MMF for twelve weeks. They showed significant decrease in the urticarial activity score. All patients were able to discontinue corticosteroids. There was also a decrease in antihistamine dose. Further controlled clinical studies are needed to determine the value of MMF in the treatment of severe CIU (110).

### CYCLOPHOSPHAMIDE

Severe CIU can be treated with several immunomodulatory drugs. In recent literature, several case reports and small studies of cyclophosphamide (CTX) in the management of chronic urticaria treatment have been published. In one of these papers, one patient with severe CIU and positive autologous serum skin test had benefit from CTX 500-1500 mg every 2-4 weeks (111). The treatment started with the initial dose of 500 mg CTX intravenously, followed by increases of 100 mg every 2 weeks, with the maximum dose reaching 1500 mg once a month. Complete clinical remission was reached in 7 months and prednisone was discontinued. Repeat intracutaneous testing to autologous serum was negative, consistent with an abrogated autoantibody response (111). Another group of authors evaluated the efficacy of H1-antihistamine, corticosteroids and CTX in the treatment of chronic dermatographic urticaria. One group of patients were treated with cetirizine hydrochloride 10 mg *per day* orally, and the other group were treated with betamethasone 2 mg, CTX 50 mg and cetirizine 10 mg *per day* for a total period of 4 weeks. The majority of patients showed relapse within 3 days of treatment discontinuation. Study results showed that treatment supplementation with oral corticosteroids or CTX was more effective in symptom control than cetirizine alone. However, four-week supplementation was not

adequate to prevent disease relapse upon drug discontinuation (112). Oral CTX has also been administered in case of cyclosporine- and steroid-resistant chronic urticaria with proven autoreactivity to autologous serum skin testing (113). The use of oral CTX has already been described in the treatment of Schnitzler's syndrome (114).

### CYCLOSPORINE

Cyclosporine (Sandimmun Neoral®) (Csa) has been widely used in the prevention and treatment of organ transplant rejection and also in autoimmune diseases. Recently, Csa has been introduced in the treatment of severe 'idiopathic' urticaria. Several authors have described good results with this therapy (105,115-117). A limited number of severe CIU patients treated with CsA have been reported in 1997 (116). It was open label study. In 2000, Grattan *et al.* treated 20 patients with CsA in a dose of 4 mg/kg/day for 4 weeks and compared it to placebo. All patients were given cetirizine 10 mg/day (117). They measured daily urticaria activity score, basophil histamine release and autologous serum skin test. Study results confirmed CsA efficacy and provided further evidence for the role of histamine-releasing autoantibodies in CIU (117).

According to Vena *et al.*, CsA was given in the initial dose of 5 mg/kg/day and progressively reduced to 3 mg/kg/day. After a week of run-in period with cetirizine 10 mg, patients were given CsA for 8 or 16 weeks. Adverse events were recorded in six patients and included elevated serum creatinine. The patient quality of life was improved (118,119). Patients with severe disease unresponsive to antihistamines and showing a positive autologous serum skin test were treated with CsA 4 mg/kg/day of CsA for 4 or 12 weeks. Prolonged use of this therapy for more than 1 month provided little benefit in terms of clinical improvement. In a double-blind study published in 2003, 40 adults were assigned randomly to receive CsA (5 mg/kg/day for 8 weeks and then 4 mg/kg/day for 8 weeks) or cetirizine (10 mg/day) and then followed up for 9 months (120). After 2 weeks, the study was opened because 16 (40%) patients had daily severe relapses requiring systemic steroid treatment. All of these patients had been receiving antihistamines and therefore were assigned to the CsA treatment regimen (5 mg/kg/day for 8 weeks and then 4 mg/kg/day for 8 weeks). Only two patients failed to complete the study because of severe symptoms occurring after 4 and 7 days of follow up and requiring long-term steroid treatment.

After 9-month follow up, 16 patients were still in full remission. These results show the long-term efficacy and tolerability of CsA in patients with severe CIU unresponsive to conventional treatment (120). Toubi *et al.* report on prolonged cyclosporin-A treatment for severe chronic urticaria (121).

Low-dose and short-term cyclosporine treatment was evaluated in patients with CIU (122). Cyclosporine in a dose of 2.5 mg/kg/day in patients with severe CIU is efficient and safe. Improved clinical efficacy and marked decreases in serum cytokine levels suggest that inhibition of cytokine generation is involved in the action of the drug in this clinical setting. After 4 weeks of CsA therapy, the mean IL-2R, TNF- $\alpha$  and IL-5 levels were significantly decreased.

CsA is a calcineurin inhibiting immunomodulatory drug (123), and it has been shown to inhibit histamine release probably by interfering with intracellular signaling following cross-linking of IgE receptor.

Many cutaneous side effects of CsA have been described, e.g., hypertrichosis, gingival hyperplasia, sebaceous gland hyperplasia and viral skin infections. One case report describes cyclosporine-induced follicular eruption (125-128). Unfortunately, CsA also has some major side effects (including nephrotoxic ones). Reversible ascending motor neuropathy as a side effect of systemic treatment with cyclosporine for nodular prurigo has been described in literature (129). When side effects of CsA are compared to tacrolimus, hypertension, hypertrichosis and gingival hyperplasia were less pronounced with tacrolimus and elevated blood glucose level was observed in the CsA group (130).

## TACROLIMUS

Cyclosporine and tacrolimus are calcineurin inhibiting immunosuppressant agents useful in the treatment of immune-mediated inflammatory dermatoses (123). Tacrolimus is a macrolide immunosuppressant drug isolated from *Streptomyces tsukubaensis* and is widely used in organ transplantation (131). Oral tacrolimus for chronic urticaria treatment has been studied in an open-label prospective study (132). Nineteen patients were treated with doses between 0.05 and 0.2 mg/kg/day divided into two daily doses for 12 weeks; 70% of patients showed clinical response to this treatment. It is important to monitor renal and liver function during therapy. Adverse events reported seem to be less pronounced or similar to those

with cyclosporine (3,130,132-134). There is a new, once-daily formulation registered as Advagraf for European Union (135).

## OMALIZUMAB

Omalizumab is a recombinant humanized monoclonal antibody against immunoglobulin IgE, and acts as a neutralizing antibody by binding IgE at the same site as the high-affinity receptor. Omalizumab is a monoclonal antibody targeting the high-affinity receptor binding site on human immunoglobulin IgE. Bound IgE is not available for basophil binding, degranulation is attenuated, and allergic symptoms are reduced. Omalizumab has been approved for the treatment of persistent allergic asthma in patients that are poorly controlled with inhaled corticosteroids (136,137). Approximately 45% of patients with chronic urticaria have an IgG autoantibody directed to the alpha-subunit of the high-affinity IgE receptor (chronic autoimmune urticaria, CAU) leading to cutaneous mast cell and basophil activation. Treatment of allergic asthma with omalizumab produces rapid reduction in free IgE levels and subsequent decrease in Fc epsilon RI expression on mast cells and basophils. If this occurs in CAU, cross-linking of IgE receptors by autoantibody would be less likely, reducing cell activation and urticaria/angioedema (138). Twelve patients with CAU were treated with placebo for 4 weeks, followed by omalizumab ( $\geq 0.016$  mg/kg/IU mL(-1) IgE *per* month) every 2 or 4 weeks for 16 weeks. Seven of twelve patients had complete symptom resolution, while one patient did not respond. Others showed improvement, but urticaria persisted (138).

Several authors report on good therapeutic response to omalizumab (139-146). Omalizumab is a steroid-sparing agent in autoimmune urticaria or CIU with angioedema (144). It has been used successfully in childhood urticaria (146). Successful treatment of cholinergic urticaria (147) and cold induced urticaria/anaphylaxis (148) with anti IgE therapy has also been published.

Recently, a few articles on allergic-like reactions to omalizumab have been published. A group of authors describe two patients. The *in vitro* and *in vivo* testing supported a conclusion that adverse reactions experienced by the two patients after more than a year of successful omalizumab therapy for asthma were most likely anaphylactoid in nature. Polysorbate, an excipient in omalizumab, is known to cause similar reactivity to other medicines and is the most likely cause of these reactions (149,150).

## STANOZOLOL

Stanozolol is an inexpensive anabolic steroid with a 30:1 anabolic:androgenic ratio. Only few papers have appeared on stanozolol in the management of chronic urticaria (151,152). A group of authors report on treatment with 2 mg stanozolol twice daily plus cetirizine 10 mg daily compared with cetirizine 10 mg daily, demonstrating that stanozolol is an effective and safe adjuvant therapy for the treatment of chronic refractory urticaria (152). The possible adverse effects include hirsutism, weight gain, menstrual irregularities or postmenopausal bleeding, acne, and mood changes (153-155).

## HYDROXYCHLOROQUINE

There are only a few articles on the use of hydroxychloroquine in the management of chronic urticaria (156-158). In 2004, the impact of hydroxychloroquine (Plaquenil; Sanofi-Synthelabo) therapy on chronic urticaria was reported. Immunomodulation with hydroxychloroquine is safe and appears to offer some efficacy as an intervention in CIU.

## PUVA CHEMOTHERAPY AND UVB THERAPY

There are little data to support the use of psoralen UVA (PUVA) photochemotherapy and UVB phototherapy for chronic urticaria (159-163). The efficacy of PUVA therapy in the management of chronic urticaria was assessed by a Canadian group of authors, and it was ranked as neutral or ineffective (164). A placebo controlled randomized trial was conducted on UVB phototherapy. Control group received antihistamine alone. Statistically significant differences were found and the authors concluded that narrow-band UVB could be an effective complementary treatment for patients with chronic urticaria (165).

## CONCLUSION

Treatment of chronic urticaria can pose a major challenge to the physician. Many patients with chronic urticaria have at least partial response to antihistamines, but there are a proportion of patients that do not, thus requiring a more aggressive treatment with different types of immunomodulatory agents. Dermatologists must be knowledgeable about the implementation of correct treatment. There is a wide range of non-pharmacological and pharmacological options and there is no universal solution, therefore the most appropriate treatment should be tailored individually for each patient.

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