

Evidence-Based Management of Chronic Urticaria in Children

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Chronic urticaria (CU) in children is a distressful disorder that can often be challenging to treat. Elimination or treatment of eliciting stimulus is the first step in the management of CU; however, in the majority of cases, the cause remains unknown. According to currently available guidelines, H1-antihistamines are still first-line therapy for CU in children. Unfortunately, regularly approved doses relieve symptoms in <50% of patients, necessitating an up to 4-fold dose increase. However, in some patients, even high doses of H1-antihistamines fail to produce satisfactory results, leaving place for new therapeutic strategies in the treatment of CU; first to add either leukotriene antagonist or H2-antihistamine. In severe, unresponsive cases, other therapeutic approaches should be considered. However, it is important to be familiar with the possible side effects, because some of these approaches imply off-label use of drugs. This review presents a summary of the evidence on the treatment of CU in pediatric patients available up to January 2012.

Introduction

CHRONIC URTICARIA (CU) is a relapsing cutaneous disease characterized by spontaneous appearance of wheals and pruritus recurring for more than 6 weeks.¹ Overall, 0.1% to 3% of children will be found to have CU.² Although manifesting cutaneously, CU may not be contained to the skin organ as comorbidities, and/or underlying systemic etiologies may be the causal disease. Despite broad diagnostic work-up, the underlying cause remains unidentified in up to 80% of patients, making causal and sometimes symptomatic treatment difficult.² According to the guidelines for the management of children with CU, the mainstay of therapy is symptomatic treatment with H1-antihistamines.³ However, regular approved doses are often not effective and require dose increase.⁴ Moreover, some patients do not respond even to very high doses, thus necessitating new therapeutic options for CU in the pediatric population. The aim of this review was to summarize currently available evidence in the management of CU in children aged up to 18 years. A case example is provided to illustrate the difficulties in the management of CU in children. Literature search was made using Medline/PubMed (until January 2012). A standard search strategy, including the following terms, was used: children, urticaria, CU, and treatment. Drug search included a group of medications (antihistamines, leukotrienes, corticosteroid, immunosuppressants, cyclosporine, dapsone, omalizumab, and diet) and specific generic medication names. References were also selected from authors' files. On the basis of abstract content, relevant articles were read specifically to provide

context for this review rather than to comprehensively catalog all publications.

Illustrative Case

A 15-year-old girl was referred to the hospital with a history of frequent relapses of generalized urticaria with pruritus during a period of 6 months. Her medical history was unremarkable, and there were no allergic or other chronic diseases in her family. Before the referral to our hospital, she was already treated with corticosteroids and H1-antihistamines, however, without clinical response. On admission, physical examination revealed no significant findings. Broad diagnostic work-up for allergic, immune, rheumatologic, autoimmune, vasculitic, malignant, physical, infectious, and neurologic causes was performed and revealed no underlying cause. Due to previous unresponsiveness to high doses of fexofenadine (480 mg daily), we decided to change it to the second-generation antihistamine cetirizine (10 mg once daily) and recommended a pseudoallergen-free diet. She suffered from relapses of generalized urticaria with pruritic hives. We increased the dose of cetirizine to 40 mg once daily, but without any benefit. No significant changes in the signs or symptoms were observed, and she had to take periodic cycles of corticosteroids. At that point, she was anxious due to relapses of urticaria, losing sleep, and skipping school, placing her and her family in great distress. We decided to start add-on therapy with montelukast orally (10 mg daily), with dramatic symptom improvement and complete resolution of urticaria in 10 days.

We continued to follow her for 7 months, and she did not experience any recurrence of urticaria, while reporting remarkable improvement in her quality of life.

Discussion

CU is rare in childhood, and no underlying cause is identifiable in most of these patients.⁵ The possible causes include physical factors, infections, foods, food additives, aeroallergens, and medications.⁶ The autoreactive nature of CU was demonstrated in 30%–50% of patients.⁷ It is possible that psychological stress can also trigger urticaria through stress-induced release of the corticotropin-releasing hormone (CRH). Papadopolou et al. found an increased number of skin CRH-R1 receptors and mast cells in patients with stress-related CU. Moreover, the activation of the CRH-R1 receptor by stress mediates cutaneous mast cell degranulation that is widely involved in CU.⁸

The wheal, which is the main characteristic of urticaria, is caused by the activation of dermal mast cells and to a lower extent of basophils.⁹ The activation can occur through both immunoglobulin (Ig)E-mediated and non-IgE-mediated mechanisms induced by various trigger factors. The final result of mast cell activation is the release of preformed (histamine and tryptase) and newly formed (prostaglandins and leukotrienes) mediators.¹⁰

CU is a long-lasting condition that significantly impairs patient quality of life, causing sleep disturbance and significantly affecting normal life activities.¹¹ Moreover, it is sometimes very challenging to treat, and when achieved, maintenance of symptom-free interval is even more challenging. On the other hand, spontaneous recovery of CU is also possible. According to Sahiner et al., resolution is seen in half of the children within 5 years. On the contrary, girls older than 10 years may have unfavorable prognosis.¹² Female gender is recognized as a poor prognostic factor in adult patients¹³; however, the reason remains unclear, speculating that hormones and higher prevalence of autoimmunity play an important role.¹⁴ Based on the studies in adults, other prognostic factors include disease severity and duration as well as the type of urticaria.¹⁵

The etiology of CU can be identified in only 25% of cases despite comprehensive investigation,¹⁶ emphasizing the importance of thorough history, including family history, and physical examination in diagnostic work-up. These specific historical considerations should direct further diagnostic work-up in all patients with CU.¹⁷ Standard therapy for CU first includes elimination or treatment of the eliciting stimulus; however, in the majority of cases, the cause remains unknown, leaving place only for symptomatic treatment.

This review aims to present currently available evidence on the treatment of CU in children and to give evidence-based grades of recommendation for specific medication groups.¹⁸ Figure 1 represents proposed algorithm for the treatment of CU in children based on published data and guidelines on the urticaria management.¹⁹

H1-antihistamines (grade of recommendation = B)

H1-antihistamines are the only drugs based on numerous randomized controlled trials with class 1 evidence in the treatment of CU in adults (Table 1).¹⁹ Although there is often tendency to consider different antihistamines as similarly

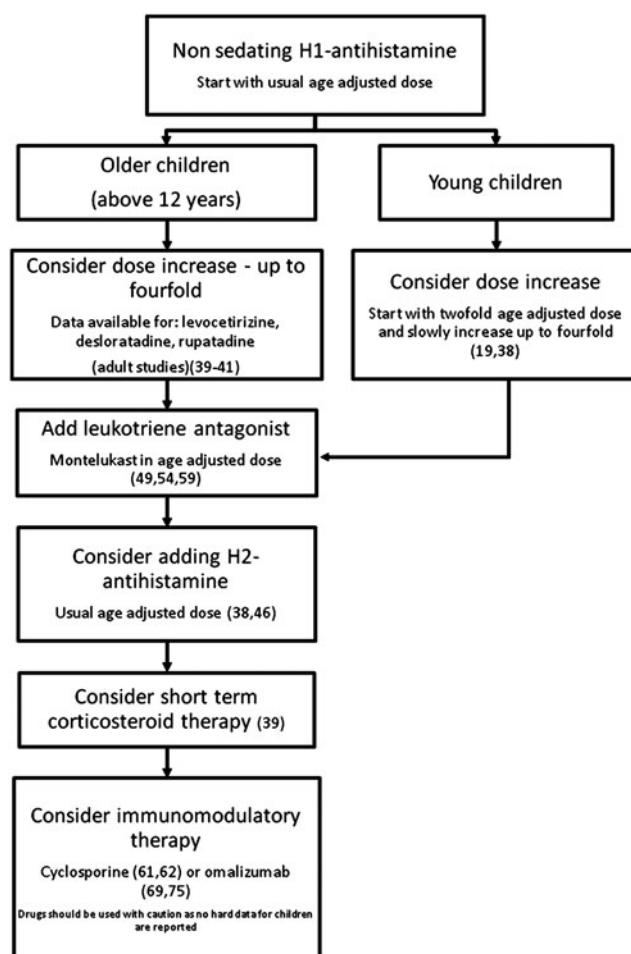


FIG. 1. Proposed algorithm for the treatment of chronic urticaria in children based on the currently available evidence and guidelines on the urticaria management (19). Algorithm contains reference on which statement is based.

efficacious, they are drugs with different potency and performance. First-generation H1-antihistamines (including chlorphenamine, diphenhydramine, hydroxyzine, and promethazine) have a high potential to cause a wide variety of adverse effects, such as sedation and anticholinergic effect.²⁰ Based on these side effects, regulation agencies from the United Kingdom and U.S. Food and Drug Administration (FDA) do not recommend their use below the age of 6 years, leaving a place for the second generation.²¹ Table 1 presents all randomized controlled trials on the role of antihistamines in the treatment of CU comparing to placebo or to other type of antihistamines.

The main mechanism of action of the antihistamines is anti-inflammatory action; they stabilize the mast cell and basophile membranes inhibiting transmembrane flux of calcium and intracellular cAMP and decreasing cytoplasmic transcription factors responsible for cytokine, chemokine, and adhesion molecule release.²² Although antihistamines are used frequently in children, only limited number of trials has been performed in this age group. The first study performed in young children was conducted by Simons et al. proved that use of H1-antihistamine in children aged 12 to 24 months is safe.²³ This study did not initially aimed to assess the efficacy of cetirizine in the treatment of urticarial

TABLE 1. RANDOMIZED CONTROLLED TRIALS ON THE ROLE H1-ANTIHISTAMINES IN THE TREATMENT OF CHRONIC URTICARIA (ADULT AND PEDIATRIC STUDIES)

<i>Author (year)</i>	<i>N (age)</i>	<i>Drug used (dose)</i>	<i>Author's conclusion</i>
Hong et al. (2010) ⁸²	64 (adults)	Desloratadine (5 mg) vs. levocetirizine (5 mg)	Desloratadine was less sedative, and levocetirizine was more efficacious
Zuberbier et al. (2010) ⁸³	525 (adults)	Bilastine (20 mg) vs. levocetirizine (5 mg) vs. placebo	Bilastine and levocetirizine equally efficacious, equally safe, and well tolerated compared with placebo
Grob et al. (2009) ⁸⁴	129 (adults)	Desloratadine (5 mg) daily or when symptoms appear	Daily therapy is a better regimen
Bachert et al. (2009) ⁸⁵	721 (12–70 years)	Bilastine (20 mg) vs. desloratadine (5 mg) vs. placebo	Bilastine 20 mg and desloratadine 5 mg equally effective and more effective than placebo
Potter et al. (2009) ⁸⁶	886 (adults)	Levocetirizine (5 mg) vs. desloratadine (5 mg)	Levocetirizine 5 mg was more efficacious than desloratadine 5 mg
Grob et al. (2007) ⁸⁷	137 (adults)	Desloratadine (5 mg) vs. placebo	Desloratadine 5 mg/day more efficacious
Dubertret et al. (2007) ⁸⁸	277 (12–65 years)	Rupatadine (5, 10 and 20 mg) vs. placebo	Rupatadine 10 and 20 mg efficacious and safe treatment
Gimenez-Arnau et al. (2007) ⁸⁹	333 (12–65 years)	Rupatadine (10 and 20 mg) vs. placebo	Both doses of Rupatadine were not superior/Rupatadine 10 mg had better adverse event profile
Spector et al. (2007) ³⁴	254 (adults)	Fexofenadine hydrochloride (180 mg) vs. placebo	Fexofenadine more efficacious
Ortonne et al. (2007) ⁹⁰	137 (adults)	Desloratadine (5 mg) vs. placebo	Desloratadine—well tolerated and superior to placebo
Pons-Guiraud et al. (2006) ⁹¹	192 (adults)	Emedastine difumarate (2 mg b.i.d.) vs. loratadine (10 mg o.d.)	Emedastine—well tolerated, and as effective as loratadine in the short-term treatment
Kapp and Pichler (2006) ⁹²	166 (adults)	Levocetirizine (5 mg) vs. placebo	Levocetirizine more efficacious
Nettis et al. (2006) ⁹³	106 (adults)	Levocetirizine (5 mg) vs. placebo	Levocetirizine more efficacious
Kaplan et al. (2005) ³⁵	163 (> 12 years)	Fexofenadine (180 mg) vs. placebo	Fexofenadine hydrochloride more efficacious
Handa et al. (2004) ⁹⁴	116 (17–65 years)	Cetirizine (10 mg) vs. fexofenadine (180 mg)	Cetirizine more efficacious than fexofenadine
Monroe et al. (2003) ⁹⁵	226 (> 12 years)	Desloratadine (5 mg) vs. placebo	Desloratadine more efficacious
La Rosa et al. (2001) ⁹⁶	62 (2–6 years)	Cetirizine (5 mg q.d.) vs. oxatamide (25 mg q.d.)	Both efficacious and safe
Ring et al. (2001) ⁹⁷	190 (12–79 years)	Desloratadine (5 mg) vs. placebo	Desloratadine more efficacious
Nelson et al. (2000) ³⁶	418 (adults)	Fexofenadine (20, 60, 120, or 240 mg) vs. placebo	All 4 fexofenadine doses were statistically superior to placebo/twice-daily doses of 60 mg or greater were most effective
Leynadier et al. (2000) ⁹⁸	61 (adults)	Mizolastine (10 mg) vs. loratadine (10 mg)	Both proved very efficacious and safe/Mizolastine demonstrated a superiority in prick tests, beneficial effects on angioedema, and seemed to provide a faster onset of action
Finn et al. (1999) ³³	439 (adults)	Fexofenadine (20, 60, 120, or 240 mg b.i.d.) vs. placebo	Fexofenadine is statistically superior to placebo/doses of ≥60 mg twice a day are most effective
Dubertret et al. (1999) ⁹⁹	247 (adults)	Mizolastine (10 mg) vs. loratadine (10 mg) vs. placebo	Mizolastine is as effective and safe as loratadine and superior to placebo
Breneman et al. (1996) ¹⁰⁰	188 (> 12 years)	Cetirizine (10 mg) vs. hydroxyzine (25 mg t.i.d.) vs. placebo	Cetirizine 10 mg o.d. was equivalent to hydroxyzine 25 mg t.i.d.
Brostoff et al. (1996) ¹⁰¹	56 (adults)	Mizolastine (10 mg) vs. placebo	Mizolastine more efficacious
Kalis (1996) ¹⁰²	211 (adults)	Ebastine (10 mg) vs. terfenadine (60 mg) vs. placebo	Ebastine—superior to placebo and similarly effective as terfenadine
Breneman et al. (1995) ¹⁰³	187 (adults)	Cetirizine (10 mg) vs. astemizole (10 mg) vs. placebo	Cetirizine and astemizole provide effective relief/clinical benefit occurs more rapidly with cetirizine
Andri et al. (1993) ¹⁰⁴	30 (> 16 years)	Cetirizine (10 mg) vs. terfenadine (60 mg b.i.d.)	Cetirizine more effective than terfenadine

(continued)

TABLE 1. (CONTINUED)

<i>Author (year)</i>	<i>N (age)</i>	<i>Drug used (dose)</i>	<i>Author's conclusion</i>
Abu Shareeah (1992) ¹⁰⁵	30 (> 16 years)	Loratadine (10 mg) vs. terfenadine (60 mg b.i.d.)	Both effective/the effect of loratadine was more pronounced, quicker in onset, and more persistent
Monroe et al. (1992) ¹⁰⁶	203 (adults)	Loratadine (10 mg q.d.) vs. hydroxyzine (25 mg t.i.d.) vs. placebo	Loratadine and hydroxyzine more effective than placebo/loratadine had less side effects
Monroe (1992) ¹⁰⁸	59 (adults)	Loratadine (10 mg) vs. hydroxyzine (25 mg, t.i.d.) vs. placebo	Loratadine is as effective as hydroxyzine/does not have the central nervous system effects
Sussman and Jancelewicz (1991) ¹⁰⁷	36 (adults)	Astemizole (10 mg) vs. diphenhydramine group (25 mg t.i.d.) vs. hydroxyzine hydrochloride (25 mg t.i.d.)	Astemizole was as effective as hydroxyzine/diphenhydramine less effective
Goh et al. (1991) ¹⁰⁹	28 (adults)	Cetirizine (10 mg) vs. placebo	Cetirizine more efficacious
Kalivas et al. (1990) ¹¹⁰	219 (adults)	Cetirizine (5 to 20 mg) vs. hydroxyzine (25 to 75 mg) vs. placebo	Cetirizine o.d. dose equivalent in efficacy to hydroxyzine in divided doses
Alomar et al. (1990) ¹¹¹	47 (adults)	Cetirizine vs. astemizole	Cetirizine superior
Belaich et al. (1990) ¹¹²	187 (adults)	Loratadine (10 mg) vs. terfenadine (60 mg b.i.d.) vs. placebo	Loratadine—more effective than placebo/clinically more effective than terfenadine
Boggs et al. (1989) ¹¹³	37 (adults)	Terfenadine (60 mg b.i.d.) vs. hydroxyzine (25 mg q.i.d.)	Terfenadine—more effective than placebo and as effective as hydroxyzine
Leyh et al. (1989) ¹¹⁴	20 (adults)	Acrivastine (8 mg and 4 mg) vs. clemastine (1 mg) vs. placebo	All active preparations—more effective than placebo
Salo et al. (1989) ¹¹⁵	21 (adults)	Acrivastine (8 mg) vs. hydroxyzine (20 mg) vs. placebo	Acrivastine and hydroxyzine—significantly better than placebo/no significant differences between the active preparations
van Joost et al. (1989) ¹¹⁶	56 (adults)	Acrivastine (8 and 4 mg) vs. terfenadine (60 mg) vs. placebo	Active preparations—significantly better than placebo
Juhlin and Arendt (1988) ¹¹⁷	30 (adults)	Cetirizine (10 mg) vs. placebo	Cetirizine—significantly better than placebo
Grant et al. (1988) ¹¹⁸	122 (adults)	Terfenadine (60 mg b.i.d.) vs. chlorpheniramine (4 mg t.i.d.) vs. placebo	Terfenadine—superior to placebo/statistical significance was not achieved for chlorpheniramine
Fox et al. (1986) ¹¹⁹	51 (adults)	Astemizole (10 mg) vs. placebo	Astemizole more efficacious
Cainelli et al. (1986) ¹²⁰	42 (adults)	Astemizole (10 mg) vs. terfenadine (120 mg)	Significant decrease in symptoms in both groups/the effect of astemizole increased with time whereas that of terfenadine decreased after 3 weeks of treatment
Ferguson et al. (1985) ¹²¹	21 (adults)	Terfenadine (60 mg b.i.d.) vs. placebo	Terfenadine more efficacious

o.d., once daily; q.d., daily; t.i.d., three times a day; b.i.d., twice daily.

symptoms; however, results revealed that only 5.8% of the children with atopic dermatitis treated for 18 months with cetirizine had one or more episodes of urticaria compared with 16.2% of the children treated with placebo.²³ The use of cetirizine in children younger than 2 years is not recommended by manufacturer. However, according to a pharmacokinetic and pharmacodynamic study of cetirizine conducted by Spicak and colleagues in children aged 6 to 24 months, it could be successfully used in infants and toddlers.²⁴ It is approved by the FDA for CU in children aged 6 months and older.²⁵ The same efficacy of the H1-antihistamines in the suppression of urticarial symptoms was confirmed by the Early Prevention of Asthma in Atopic Children Study, which aimed to assess the efficacy of using levocetirizine.²⁶ According to this study, long-term use of levocetirizine prevents and treats urticaria in young children. Furthermore, Hampel et al. showed that levocetirizine is well tolerated even in younger children with CU, aged 6 months and above.²⁷ However, this study evaluated only safety of levocetirizine for young children, and unfortunately did not report its efficacy in the treatment of CU in this age group.

Other studied antihistamines include loratadine, which is licensed for the treatment of CU in children of 2 years and older.²² Loratadine was tested in children aged 6 to 12 years with different chronic allergic skin diseases (mostly atopic dermatitis) and showed relief of symptoms in 45% of patients; however, 6% reported different side effects, including sedation, nausea, vomiting, fever, and fatigue.²⁸ These side effects could be avoided by using loratadine's active metabolite, desloratadine, which has 2.5–4 times more antihistaminic potency than loratadine.²⁹ Its use has not been connected with sedation or cognitive impairment.³⁰ Safety of desloratadine was investigated in children older than 2 years of age and proved to be safe with a similar incidence of adverse events in treatment and placebo groups.³¹ Fexofenadine, another derivative of second-generation antihistamine (terfenadine), is also approved by the FDA for CU in children aged 6 months and older.³² There are no studies on the role of fexofenadine in the treatment of CU in children; however, studies on adults proved its efficacy.^{33–36} Moreover, safety of fexofenadine has been tested in children with allergic rhinitis.³⁷

Unfortunately, the treatment with regular approved doses of H1-antihistamines relieves symptoms effectively in less than half of patient with CU.⁴ In patients who do not experience the benefit of regular antihistamine doses, a dose increase for up to 4-fold could be recommended.^{1,4,38–41} However, beside recommendation by the experts and available guidelines,^{19,38} there is no evidence in children, especially in young children. Based on these data, escalation in the dose could be easily recommended for older children (mostly above 12 years of age) who use same medication dose as adults. For younger children, age-adjusted dose escalation could be considered, but with caution and monitoring for possible side effects. Moreover, some patients do not respond even to very high doses necessitating new therapeutic options.

H2-antihistamines (grade of recommendation=C)

Skin blood vessels have both H1 and H2 receptors, the activation of which induces formation of wheal and erythema; however, that phenomenon is only limitedly influenced

by the sole activation of H2 receptors.²² There are some evidence (all based on studies in adults) that a combination of H1- and H2-antihistamines provides better symptom control than H1 agents alone.^{42–45} Some pediatric authorities also suggest adding an H2-antihistamine in unresponsive patients, but not for routine disease control.³⁸ Regarding safety, H2-antihistamines have been used in children for a long time, and based on currently available evidence, the FDA has approved ranitidine use in children older than 1 month.⁴⁶

Antileukotrienes (grade of recommendation=C)

It has been established that other factors such as kinins, prostaglandins, and leukotrienes play an important role in the pathophysiology cascade of urticaria; they prolong the inflammatory process of allergic reaction, influencing a poor response of symptoms to antihistamine treatment in some patients.⁴ Considering the important role of leukotrienes in the pathophysiological mechanisms of allergic inflammation, the leukotriene receptors antagonists, montelukast and zafirlukast, have recently been proposed for urticaria treatment.⁴⁷ They can be used as monotherapy or in combination with H1 receptor antagonists. Currently available evidence on the role of montelukast in the treatment of CU is scarce (Table 2). Of all published trials, 6 studies included montelukast in the treatment of CU, however, with contradictory results and no strict recommendation.^{48–52} All montelukast studies included adults, and only 3 studies also included pediatric patients.^{49,53,54} Erbagci demonstrated montelukast to be effective and safe in the treatment of refractory chronic idiopathic urticaria.⁴⁸ The study performed by Nettis et al. included patients above 15 years of age and found a combination of desloratadine plus montelukast to be effective in the treatment of relatively mild CU.⁴⁹ On contrary, treatment with zafirlukast alone proved to be inefficient in the treatment of CU,⁵⁵ and the benefit could be expected in patients with autoimmune CU refractory to H1-antihistamines when zafirlukast is used as add-on therapy.^{53,56} To the best of our knowledge, there are no studies on the role of antileukotrienes in the treatment of CU exclusively in children. Literature search yielded one case report presenting a 10-year-old boy who stayed symptom-free on combined treatment with antifibrinolytic agent (aminocaproic acid), montelukast, and ranitidine.⁵⁷ The authors suggest adding this combination in the treatment of CU, emphasizing its steroid-sparing effect. Conclusively, the available results on the efficacy of antileukotrienes are quite inconsistent. Based on the currently available evidence, antileukotrienes should only be used as add-on therapy.⁵⁸ Of these, montelukast and zafirlukast are FDA-approved for the prophylaxis of asthma in children from the age of 12 months and 5 years, respectively.⁵⁹

Other options and novel therapies

The proof for the autoreactive nature of CU offers the possibility of immunomodulatory or immunosuppressive therapy, but only after the established treatment options have been exhausted.⁶⁰ Short-term use of oral corticosteroids (grade of recommendation=D) may be necessary in some children with severe form of the disease, but long-term oral corticoids should not be used in children with CU.³⁹ Other agents include cyclosporine, dapsone, and omalizumab.

TABLE 2. RANDOMIZED CONTROLLED TRIALS ON THE ROLE OF ANTILEUKOTRIENES IN THE TREATMENT OF CHRONIC URTICARIA

<i>Author (year)</i>	<i>N (age)</i>	<i>Drugs (dose)</i>	<i>Author's conclusion</i>
Wan (2009) ⁵¹	120 (adults)	Hydroxyzine (25 mg) + cetirizine (5 mg b.i.d.) vs. hydroxyzine (25 mg) + famotidine (20 mg b.i.d.) vs. hydroxyzine (25 mg b.i.d.) + montelukast (5 mg b.i.d.) vs. placebo	All 3 treatment groups revealed significant difference comparing to placebo
Godse (2006) ¹²²	20 (adults)	Montelukast (10 mg) vs. cetirizine (10 mg)	Study not completed—montelukast group of patients showed no control of symptoms
Di Lorenzo et al. (2004) ⁵⁰	160 (adults)	Desloratadine (5 mg) vs. desloratadine (5 mg) + montelukast (10 mg) vs. montelukast (10 mg) vs. placebo	Desloratadine is highly effective for the treatment CU/combined therapy of desloratadine + montelukast does not offer a substantial advantage
Nettis et al. (2004) ⁴⁹	81 (15 to 71 years)	Desloratadine (5 mg) vs. desloratadine (5 mg) + montelukast (10 mg) vs. placebo	Desloratadine + montelukast improve the symptoms significantly more than desloratadine/did not have a significant effect on the number of urticarial episodes
Bagenstose et al. (2003) ⁵³	95 (>12 years)	Cetirizine (10 mg) + zafirlukast (20 mg b.i.d.) vs. cetirizine (10 mg) + placebo	Combination therapy demonstrated a modest, but significantly greater improvement compared with cetirizine monotherapy
Erbagci (2002) ⁴⁸	30 (adults)	Montelukast (10 mg) + cetirizine when needed vs. placebo + cetirizine when needed	Montelukast therapy—significant _decreases in urticaria activity scores/H1-antihistamine use significantly less frequent during the montelukast treatment
Reimers et al. (2002) ⁵⁵	52 (adults)	Zafirlukast (20 mg b.i.d.) vs. placebo	Zafirlukast—no significant positive effect comparing to placebo
Pacor (2001) ⁵⁴	51 (15–71 years)	Montelukast (10 mg) vs. cetirizine (10 mg) vs. placebo	Montelukast is more effective for the treatment CU than placebo or cetirizine

CU, chronic urticaria.

Data on the use of cyclosporine (grade of recommendation=D) in pediatric patients are scarce^{61,62}; Doshi et al. present a series of cases ($n=7$, aged 9–16 years) with refractory CU treated with cyclosporine at a dose of 3 mg/kg/day, resulting in resolution of symptoms in all patients.⁶¹ Dapsone (grade of recommendation=D), member of the sulfones family, exerts anti-inflammatory effects through inhibiting neutrophil chemotactic migration, protects cells from inflammation-mediated injury, and reduces the release of prostaglandins and leukotrienes.⁶³ There are several reports on the role of dapsone in the treatment of CU showing promising effect.^{64–66} Dapsone has been used in children for other, mostly dermatological diseases.⁶⁷ However, there is no evidence for the safety and efficacy in children with CU.

Omalizumab (grade of recommendation=D) blocks the binding of IgE to the FcεRI receptor on IgE effector cells and stops mast cell and basophil activation.⁶⁸ There is an increasing body of evidence for the beneficial role of omalizumab in the treatment of severe, H1-antihistamine unresponsive CU in adults.^{69–74} One of these trials also included children older than 12 years of age.⁶⁹ It was a randomized controlled trial comparing 3 different doses of omalizumab (75, 300, and 600 mg) with placebo in patients staying symptomatic despite treatment with H1-antihistamines. The absolute mean decrease in the urticaria activity score in the groups receiving 300 and 600 mg was significantly greater compared to the placebo

group; however, there was no significant difference for 75 mg dose. None of the placebo group patients achieved complete resolution of symptoms.

Moreover, omalizumab has been safely used in children with asthma older than 6 years of age.⁷⁵ However, strong evidence is needed for its recommendation in the treatment of pediatric CU.

Apart from pharmacological treatment, a low pseudoallergen-free diet can be tried in those suffering from CU (grade of recommendation=D). It is estimated that pseudoallergens induce and/or aggravate urticaria in some patients.⁷⁶ These substances include artificial preservatives, colorings, and flavors.⁷⁷ Results of several studies performed in adults support the effectiveness of a pseudoallergen-free diet in reducing CU symptoms.^{77–80} According to the study by Magerl et al., which excluded pediatric patients from the analysis, 1 of 3 patients will clinically benefit from the diet.⁸¹ However, this study was not a randomized, placebo-controlled study, and although pediatric patients participated, their data were not included into analysis, and therefore results should be considered with caution. On the other hand, it could be argued that this diet has no adverse effects and is cost free. Thus, a 3-week trial of this diet could be one of the recommendations to a new, especially adult, patient with CU. However, as there are no studies including children, no strict recommendation can be given.

Conclusion

CU in children is a disorder with negative influence on the patient quality of life, and the management of which is still, in most cases, frustrating. Regardless of its prevalence, evidence-based data concerning clinical management in pediatric population are still limited. H1-antihistamines proved to be efficacious for symptom relief in many adult-controlled trials and are still mainstay therapy for adults and children. If no response has been achieved, the dose should be increased. Second-line regimens include adding an antileukotriene or H2-antihistamine. In severe cases, there is a place for novel, often immunosuppressive, and immunomodulatory therapy. However, as trials in children are scarce, higher-grade recommendations are still expected from pediatric randomized controlled trials. It is important for the clinicians to be familiar with the possible side effects, as recommendations sometimes, besides antihistamines, relate to the use of drugs often not approved for either CU indication or not approved for use in young children in general.

Author Disclosure Statement

All authors have stated that they have no conflict of interest.

References

- Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007; 157:1116–1123.
- Kaplan AP. Clinical practice. Chronic urticaria and angioedema. *N Engl J Med* 2002; 346:175–179.
- Powell RJ, Du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy* 2007; 37:631–650.
- Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011; 66:317–330.
- Dodig S, Richter D. Chronic autoimmune urticaria in children. *Acta Dermatovenerol Croat* 2008; 16:65–71.
- Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy* 1992; 69:61–65.
- Brunetti L, Francavilla R, Miniello VL, Platzer MH, Rizzi D, Lospalluti ML, et al. High prevalence of autoimmune urticaria in children with chronic urticaria. *J Allergy Clin Immunol* 2004; 114:922–927.
- Papadopoulou N, Kalogeromitros D, Staurianean NG, Tiblalex D, Theoharides TC. Corticotropin-releasing hormone receptor-1 and histidine decarboxylase expression in chronic urticaria. *J Invest Dermatol* 2005; 125:952–955.
- Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004; 114:465–474; quiz 475.
- Poonawalla T, Kelly B. Urticaria: a review. *Am J Clin Dermatol* 2009; 10:9–21.
- Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; 155:145–151.
- Sahiner UM, Civelek E, Tuncer A, Yavuz ST, Karabulut E, Sackesen C, et al. Chronic urticaria: etiology and natural course in children. *Int Arch Allergy Immunol* 2011; 156:224–230.
- Gregoriou S, Rigopoulos D, Katsambas A, Katsarou A, Papaioannou D, Gkouvi A, et al. Etiologic aspects and prognostic factors of patients with chronic urticaria: nonrandomized, prospective, descriptive study. *J Cutan Med Surg* 2009; 13:198–203.
- Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol* 2012; 129:1307–1313.
- van der Valk PG, Moret G, Kiemeny LA. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. *Br J Dermatol* 2002; 146:110–113.
- Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol* 1998; 134:1575–1580.
- The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. Joint Task Force on Practice Parameters. *Ann Allergy Asthma Immunol* 2000; 85(6 Pt 2):521–544.
- Oxford Centre for Evidence-Based Medicine. www.cebm.net/index.aspx?o=1025
- Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau AM, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64:1427–1443.
- Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy* 2010; 65:459–466.
- Sharfstein JM, North M, Serwint JR. Over the counter but no longer under the radar—pediatric cough and cold medications. *N Engl J Med* 2007; 357:2321–2324.
- Jauregui I, Ferrer M, Montoro J, Davila I, Bartra J, del Cuvillo A, et al. Antihistamines in the treatment of chronic urticaria. *J Investig Allergol Clin Immunol* 2007; 17 Suppl 2:41–52.
- Simons FE. Prevention of acute urticaria in young children with atopic dermatitis. *J Allergy Clin Immunol* 2001; 107:703–706.
- Spicak V, Dab I, Hulhoven R, Desager JP, Klanova M, de Longueville M, et al. Pharmacokinetics and pharmacodynamics of cetirizine in infants and toddlers. *Clin Pharmacol Ther* 1997; 61:325–330.
- www.drugs.com/pro/cetirizine.html
- Simons FE. H1-antihistamine treatment in young atopic children: effect on urticaria. *Ann Allergy Asthma Immunol* 2007; 99:261–266.
- Hampel F, Ratner P, Haeusler JM. Safety and tolerability of levocetirizine dihydrochloride in infants and children with allergic rhinitis or chronic urticaria. *Allergy Asthma Proc* 2010; 31:290–295.
- Lutsky BN, Schuller JL, Cerio R, Chieira ML, Giannetti A, Goncalves HM, et al. Comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of chronic allergic skin diseases in a pediatric population. *Arzneimittelforschung* 1993; 43:1196–1199.
- Anthes JC, Gilchrist H, Richard C, Eckel S, Hesk D, West RE, Jr., et al. Biochemical characterization of desloratadine, a potent antagonist of the human histamine H(1) receptor. *Eur J Pharmacol* 2002; 449:229–237.
- Monroe EW. Desloratadine for the treatment of chronic urticaria. *Skin Ther Lett* 2002; 7:1–2, 5.
- Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. *Curr Med Res Opin* 2004; 20:1959–1965.
- www.drugs.com/pro/fexofenadine.html
- Finn AF, Jr., Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1999; 104:1071–1078.
- Spector SL, Shikar R, Harding G, Meeves S, Leahy MJ. The effect of fexofenadine hydrochloride on productivity and quality of life in patients with chronic idiopathic urticaria. *Cutis* 2007; 79:157–162.

35. Kaplan AP, Spector SL, Meeves S, Liao Y, Varghese ST, Georges G. Once-daily fexofenadine treatment for chronic idiopathic urticaria: a multicenter, randomized, double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 2005; 94: 662–669.
36. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2000; 84:517–522.
37. Hampel FC, Kittner B, van Bavel JH. Safety and tolerability of fexofenadine hydrochloride, 15 and 30 mg, twice daily in children aged 6 months to 2 years with allergic rhinitis. *Ann Allergy Asthma Immunol* 2007; 99:549–554.
38. Zitelli KB, Cordoro KM. Evidence-based evaluation and management of chronic urticaria in children. *Pediatr Dermatol* 2011; 28:629–639.
39. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol* 2010; 125:676–682.
40. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol* 2009; 123:672–679.
41. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol* 2009; 23:1088–1091.
42. Bleehen SS, Thomas SE, Greaves MW, Newton J, Kennedy CT, Hindley F, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *Br J Dermatol* 1987; 117:81–88.
43. Monroe EW, Cohen SH, Kalbfleisch J, Schulz CI. Combined H1 and H2 antihistamine therapy in chronic urticaria. *Arch Dermatol* 1981; 117:404–407.
44. Simons FE, Sussman GL, Simons KJ. Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *J Allergy Clin Immunol* 1995; 95:685–693.
45. Paul E, Bodeker RH. Treatment of chronic urticaria with terfenadine and ranitidine. A randomized double-blind study in 45 patients. *Eur J Clin Pharmacol* 1986; 31:277–280.
46. www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf
47. Vena GA, Cassano N, Buquicchio R, Ventura MT. Anti-inflammatory effects of H1-antihistamines: clinical and immunological relevance. *Curr Pharm Des* 2008; 14:2902–2911.
48. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol* 2002; 110:484–488.
49. Nettis E, Colanardi MC, Paradiso MT, Ferrannini A. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy* 2004; 34:1401–1407.
50. Di Lorenzo G, Pacor ML, Mansueto P, Esposito Pellitteri M, Lo Bianco C, Ditta V, et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. *J Allergy Clin Immunol* 2004; 114:619–625.
51. Wan KS. Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria. *J Dermatolog Treat* 2009; 20:194–197.
52. Kosnik M, Subic T. Add-on montelukast in antihistamine-resistant chronic idiopathic urticaria. *Respir Med* 2011; 105 Suppl 1:S84–S88.
53. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. *J Allergy Clin Immunol* 2004; 113:134–140.
54. Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* 2001; 31:1607–1614.
55. Reimers A, Pichler C, Helbling A, Pichler WJ, Yawalkar N. Zafirlukast has no beneficial effects in the treatment of chronic urticaria. *Clin Exp Allergy* 2002; 32:1763–1768.
56. Nettis E, Pannofino A, Cavallo E, Ferrannini A, Tursi A. Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria. *J Allergy Clin Immunol* 2003; 112:212–213.
57. Vita D, Passalacqua G, Caminiti L, Barberio G, Pajno GB. Successful combined therapy for refractory chronic urticaria in a 10-year-old boy. *Allergy* 2004; 59:1021–1022.
58. Kanani A, Schellenberg R, Warrington R. Urticaria and angioedema. *Allergy Asthma Clin Immunol* 2011; 7 Suppl 1:S9.
59. Liu AH, Covar RA, Spahn JD, Leung DYM. Childhood asthma. In: Kliegman RM, Behrman RE, Stanton BF, St. Geme J, Schor N, eds. *Nelson Textbook of Pediatrics*, 19th ed. Philadelphia: Elsevier Saunders Co, 2011.
60. Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs* 2004; 64:2515–2536.
61. Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. *Pediatr Dermatol* 2009; 26:409–413.
62. Giuliodori K, Ganzetti G, Campanati A, Simonetti O, Marconi B, Offidani A. A non-responsive chronic autoimmune urticaria in a 12-year-old autistic girl treated with cyclosporin. *J Eur Acad Dermatol Venereol* 2009; 23:619–620.
63. Zhu YL, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol* 2001; 45:420–434.
64. Cassano N, D'Argento V, Filotico R, Vena GA. Low-dose dapsone in chronic idiopathic urticaria: preliminary results of an open study. *Acta Derm Venereol* 2005; 85:254–255.
65. Engin B, Ozdemir M. Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2008; 22:481–486.
66. Criado RF, Criado PR, Martins JE, Valente NY, Michalany NS, Vasconcellos C. Urticaria unresponsive to antihistaminic treatment: an open study of therapeutic options based on histopathologic features. *J Dermatolog Treat* 2008; 19:92–96.
67. Gurcan H, Mabrouk D, Razzaque Ahmed A. Management of pemphigus in pediatric patients. *Minerva Pediatr* 2011; 63:279–291.
68. Oliver JM, Tarleton CA, Gilmartin L, Archibeque T, Qualls CR, Diehl L, et al. Reduced FcεpsilonRI-mediated release of asthma-promoting cytokines and chemokines from human basophils during omalizumab therapy. *Int Arch Allergy Immunol* 2010; 151:275–284.
69. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011; 128:567–573.e1.
70. Spector SL, Tan RA. Therapeutic alternatives for chronic urticaria: additional reports on omalizumab. *Ann Allergy Asthma Immunol* 2008; 101:647.
71. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2007; 99:190–193.
72. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008; 122:569–573.

73. Magerl M, Staubach P, Altrichter S, Ardelean E, Krause K, Metz M, et al. Effective treatment of therapy-resistant chronic spontaneous urticaria with omalizumab. *J Allergy Clin Immunol* 2010; 126:665–666.
74. Buyukozturk S, Gelincik A, Demirturk M, Kocaturk E, Colakoglu B, Dal M. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: a real life survey. *J Dermatol* 2012; 39:439–442.
75. Milgrom H, Fowler-Taylor A, Vidaurre CF, Jayawardene S. Safety and tolerability of omalizumab in children with allergic (IgE-mediated) asthma. *Curr Med Res Opin* 2011; 27:163–169.
76. Charlesworth EN. Chronic urticaria: background, evaluation, and treatment. *Curr Allergy Asthma Rep* 2001; 1:342–347.
77. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. *Acta Derm Venereol* 1995; 75:484–487.
78. Guida B, De Martino CD, De Martino SD, Tritto G, Patella V, Trio R, et al. Histamine plasma levels and elimination diet in chronic idiopathic urticaria. *Eur J Clin Nutr* 2000; 54:155–158.
79. Di Lorenzo G, Pacor ML, Mansueto P, Martinelli N, Esposito-Pellitteri M, Lo Bianco C, et al. Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. *Int Arch Allergy Immunol* 2005; 138:235–242.
80. Hausteiner UF. Pseudoallergen-free diet in the treatment of chronic urticaria. *Acta Derm Venereol* 1996; 76:498–499.
81. Magerl M, Pisarevskaja D, Scheufele R, Zuberbier T, Maurer M. Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial. *Allergy* 2010; 65:78–83.
82. Hong JB, Lee HC, Hu FC, Chu CY. A randomized, double-blind, active-controlled, parallel-group pilot study to compare the efficacy and sedative effects of desloratadine 5 mg with levocetirizine 5 mg in the treatment of chronic idiopathic urticaria. *J Am Acad Dermatol* 2010; 63:e100–e102.
83. Zuberbier T, Oanta A, Bogacka E, Medina I, Wesel F, Uhl P, et al. Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study. *Allergy* 2010; 65:516–528.
84. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. *Allergy* 2009; 64:605–612.
85. Bachert C, Kuna P, Sanquer F, Ivan P, Dimitrov V, Gorina MM, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy* 2009; 64:158–165.
86. Potter PC, Kapp A, Maurer M, Guillet G, Jian AM, Hauptmann P, et al. Comparison of the efficacy of levocetirizine 5 mg and desloratadine 5 mg in chronic idiopathic urticaria patients. *Allergy* 2009; 64:596–604.
87. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. Quality of life in adults with chronic idiopathic urticaria receiving desloratadine: a randomized, double-blind, multicentre, placebo-controlled study. *J Eur Acad Dermatol Venereol* 2008; 22:87–93.
88. Dubertret L, Zalupca L, Cristodoulo T, Benea V, Medina I, Fantin S, et al. Once-daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study. *Eur J Dermatol* 2007; 17:223–228.
89. Gimenez-Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, Poop G, et al. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study. *Allergy* 2007; 62:539–546.
90. Ortonne JP, Grob JJ, Auquier P, Dreyfus I. Efficacy and safety of desloratadine in adults with chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, multicenter trial. *Am J Clin Dermatol* 2007; 8:37–42.
91. Pons-Guiraud A, Nekam K, Lahovsky J, Costa A, Piacentini A. Emedastine difumarate versus loratadine in chronic idiopathic urticaria: a randomized, double-blind, controlled European multicentre clinical trial. *Eur J Dermatol* 2006; 16:649–654.
92. Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. *Int J Dermatol* 2006; 45:469–474.
93. Nettis E, Colanardi MC, Barra L, Ferrannini A, Vacca A, Tursi A. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; 154:533–538.
94. Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. *J Dermatolog Treat* 2004; 15:55–57.
95. Monroe E, Finn A, Patel P, Guerrero R, Ratner P, Bernstein D. Efficacy and safety of desloratadine 5 mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2003; 48:535–541.
96. La Rosa M, Leonardi S, Marchese G, Corrias A, Barberio G, Oggiano N, et al. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children. *Ann Allergy Asthma Immunol* 2001; 87:48–53.
97. Ring J, Hein R, Gauger A. Desloratadine in the treatment of chronic idiopathic urticaria. *Allergy* 2001; 56 Suppl 65:28–32.
98. Leynadier F, Duarte-Risselin C, Murrieta M. Comparative therapeutic effect and safety of mizolastine and loratadine in chronic idiopathic urticaria. URTILOR study group. *Eur J Dermatol* 2000; 10:205–211.
99. Dubertret L, Murrieta Aguttes M, Tonet J. Efficacy and safety of mizolastine 10 mg in a placebo-controlled comparison with loratadine in chronic idiopathic urticaria: results of the MILOR Study. *J Eur Acad Dermatol Venereol* 1999; 12:16–24.
100. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother* 1996; 30:1075–1079.
101. Brostoff J, Fitzharris P, Dunmore C, Theron M, Blondin P. Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria. *Allergy* 1996; 51:320–325.
102. Kalis B. Double-blind multicentre comparative study of ebastine, terfenadine and placebo in the treatment of chronic idiopathic urticaria in adults. *Drugs* 1996; 52 Suppl 1:30–34.
103. Breneman D, Bronsky EA, Bruce S, Kalivas JT, Klein GL, Roth HL, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. *J Am Acad Dermatol* 1995; 33(2 Pt 1):192–198.
104. Andri L, Senna GE, Betteli C, Givanni S, Andri G, Lombardi C, et al. A comparison of the efficacy of cetirizine and terfenadine. A double-blind, controlled study of chronic idiopathic urticaria. *Allergy* 1993; 48:358–365.
105. Abu Shareeah AM. Comparative efficacy of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Int J Dermatol* 1992; 31:355–356.
106. Monroe EW, Bernstein DI, Fox RW, Grabiec SV, Honsinger RW, Kalivas JT, et al. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria. *Arzneimittelforschung* 1992; 42:1119–1121.
107. Sussman G, Jancelewicz Z. Controlled trial of H1 antagonists in the treatment of chronic idiopathic urticaria. *Ann Allergy* 1991; 67:433–439.
108. Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. *Clin Ther* 1992; 14:17–21.
109. Goh CL, Wong WK, Lim J. Cetirizine vs placebo in chronic idiopathic urticaria—a double blind randomised cross-over study. *Ann Acad Med Singapore* 1991; 20:328–330.
110. Kalivas J, Breneman D, Tharp M, Bruce S, Bigby M. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol* 1990; 86(6 Pt 2):1014–1018.
111. Alomar A, De La C, Fernandez J. Cetirizine vs astemizole in the treatment of chronic idiopathic urticaria. *J Int Med Res* 1990; 18:358–365.

112. Belaich S, Bruttman G, DeGreef H, Lachapelle JM, Paul E, Pedrali P, et al. Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Ann Allergy* 1990; 64(2 Pt 2):191–194.
113. Boggs PB, Ellis CN, Grossman J, Washburne WF, Gupta AK, Ball R, et al. Double-blind, placebo-controlled study of terfenadine and hydroxyzine in patients with chronic idiopathic urticaria. *Ann Allergy* 1989; 63(6 Pt 2):616–620.
114. Leyh F, Harvey SG, Gibson JR, Manna VK. A comparison of acrivastine versus clemastine and placebo in the treatment of patients with chronic idiopathic urticaria. *J Int Med Res* 1989; 17 Suppl 2:22B–24B.
115. Salo OP, Harvey SG, Calthrop JG, Gibson JR. A comparison of acrivastine versus hydroxyzine and placebo in the treatment of chronic idiopathic urticaria. *J Int Med Res* 1989; 17 Suppl 2: 18B–21B.
116. van Joost T, Blog FB, Westerhof W, Jansen FC, Starink TM, den Boer MS, et al. A comparison of acrivastine versus terfenadine and placebo in the treatment of chronic idiopathic urticaria. *J Int Med Res* 1989; 17 Suppl 2:14B–17B.
117. Juhlin L, Arendt C. Treatment of chronic urticaria with cetirizine dihydrochloride a non-sedating antihistamine. *Br J Dermatol* 1988; 119:67–71.
118. Grant JA, Bernstein DI, Buckley CE, Chu T, Fox RW, Rocklin RE, et al. Double-blind comparison of terfenadine, chlorpheniramine, and placebo in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1988; 81:574–579.
119. Fox RW, Lockey RF, Bukantz SC, Serbousek D. The treatment of mild to severe chronic idiopathic urticaria with astemizole: double-blind and open trials. *J Allergy Clin Immunol* 1986; 78:1159–1166.
120. Cainelli T, Seidenari S, Valsecchi R, Mosca M. Double-blind comparison of astemizole and terfenadine in the treatment of chronic urticaria. *Pharmatherapeutica* 1986; 4:679–686.
121. Ferguson J, MacDonald KJ, Kenicer KJ. Terfenadine and placebo compared in the treatment of chronic idiopathic urticaria: a randomised double-blind study. *Br J Clin Pharmacol* 1985; 20:639–641.
122. Godse KV. Oral montelukast monotherapy is ineffective in chronic idiopathic urticaria: a comparison with oral cetirizine. *Indian J Dermatol Venereol Leprol* 2006; 72:312–314.

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