

Review

Chronic idiopathic urticaria for the generalist

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Abstract

Chronic idiopathic urticaria (CIU) manifests as frequently occurring, short-lived wheals, surrounded by a bright-red flare, and often accompanied by angioedema. The cause of CIU is undefined and its diagnosis requires exclusion of other conditions with somewhat similar symptoms. Recent evidence has indicated that IgG autoantibodies directed against high-affinity IgE receptors (FcεRI) may be involved in the pathophysiology of CIU. Following the release of mast cell or basophil-derived histamine, this mediator binds to H₁ and H₂ receptors, leading to vasodilatation and increased vascular permeability. Individuals with CIU may be unable to conduct normal daily activities; therefore, prompt initiation of effective treatment is essential. General management of patients should include avoidance of substances likely to trigger or intensify episodes. Treatment with antihistamines is the mainstay of pharmacotherapy for CIU. Selection of antihistamine therapy for patients with CIU should be based on the following key properties: (1) proven clinical efficacy in providing a high rate of symptom improvement, (2) rapid onset of action and a long-lasting response, and (3) an excellent safety profile and a high degree of tolerability. The benefit of some second-generation antihistamines is limited by sedation, drug–drug interactions, or a variable therapeutic response. The H₁-receptor antagonist desloratadine is a new, once-daily treatment option that is potent and nonsedating, and has a low potential for drug–drug interactions. Desloratadine has a rapid onset of action and has been shown to effectively and safely reduce pruritus and the number and size of hives in patients with CIU, leading to improvements in quality of life.

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Keywords: Antihistamine; Desloratadine; Efficacy; Review; Safety; Sedation; Urticaria**1. Introduction**

Chronic idiopathic urticaria (CIU) is a challenging disease for physicians because its etiology and diagnosis can be difficult to determine, and optimal therapy must often be tailored individually for patients. Although CIU can be a debilitating disease, it is rarely life threatening; however, some of its physical manifestations (e.g. angioedema, lingual swelling) can cause patients great concern and suffering [1]. The exact incidence or prevalence of CIU remains largely unknown, although the condition is believed to affect from 0.1 to 3% of the general population [2].

In general, chronic urticaria is primarily a disease of

adults and is often initially diagnosed in persons from 20 to 45 years of age [3]. Women are twice as likely as men to have the disease [1]. CIU is characterized by the occurrence of widespread daily or near-daily wheals that occur consistently for a minimum of 6 weeks (individual wheals usually disappear within 12–24 h) [1]. The disease is characterized by remitting and relapsing bouts of urticaria (e.g. days, weeks, or months between exacerbations) [4]. Natural history studies suggest that an estimated 40% of patients with active chronic urticaria lasting at least 6 months will continue to have wheals 10 years later [5].

Chronic urticaria is classified as CIU, physical urticaria, or urticarial vasculitis [4]. In chronic urticaria, a specific trigger is not determined in approximately 75% of patients [5]; it is usually not determined for most patients with CIU. Before a diagnosis of chronic urticaria can be made, a detailed history and physical examination should be

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performed to eliminate identifiable causes of symptoms, which can include medications, occupational exposure, insect bites or stings, physical hypersensitivity (e.g. cold, heat, exercise), and hypersensitivity to food. Specific allergen challenge tests should be undertaken only by physicians experienced in the interpretation of the results and in dealing with any adverse events that may occur as a result of the challenge test [6].

Because CIU and physical urticaria (i.e. symptomatic dermatographism, delayed pressure urticaria) often coexist, physicians need to assess patients for delayed pressure urticaria before diagnosing CIU [1]. The principal clinical features and recommended diagnostic tests, which differentiate chronic urticaria from physical urticarias, are summarized in Table 1 [1]. Other common conditions must also be excluded in patients who present with urticarial symptoms, including urticarial vasculitis (Table 2), systemic lupus erythematosus, and Sjögren's syndrome [1]. Urticarial vasculitis should be suspected when individual wheals persist for longer than 24 h [1].

Chronic urticaria can cause marked disability. Individuals afflicted with chronic urticaria experience a decreased quality of life that can include a poor self-image and the inability to work or conduct normal activities (e.g. hobbies, recreation) [7]. Patients suffering from urticaria have reported considerable loss of energy, sleep disturbances, and emotional turmoil; more than 56% of patients

experience difficulties with daily living [7]. The unpredictable nature of the episodes and the consequent social restrictions may be particularly bothersome. For these reasons, early diagnosis and prompt initiation of effective treatment are essential to reduce the burden of this disease.

The goals of this article are as follows: (1) to review the clinical manifestations and systemic features of CIU, (2) to discuss key elements involved in the pathophysiology of CIU, (3) to summarize the general approach to management of patients with CIU, and (4) to review the advantages and disadvantages of both old and new pharmacologic therapeutic options. This article highlights the mainstays of therapy for the treatment of CIU, including the next-generation nonsedating antihistamine, desloratadine [4].

2. Clinical manifestations

The key clinical feature of urticaria that distinguishes it from other types of inflammatory eruptions is the frequent occurrence of short-lived (<24 h), cutaneous, erythematous wheals accompanied by itching, which can recur daily for up to 6 weeks [1,4]. Wheals associated with chronic urticaria are smooth, edematous, pink or red, and surrounded by a bright-red flare (Fig. 1) [1]. The wheals range in size from a few millimeters to several centimeters, and it is not uncommon for wheals to coalesce into larger

Table 1
Classification and features of common types of chronic urticaria

Type of urticaria	Patient age range (years)	Clinical features	Associated angioedema	Diagnostic test
Chronic idiopathic urticaria	20–50	Profuse or sparse generalized, pink or pale edematous papules or wheals, often annular with itching	Yes	–
Symptomatic dermatographism	20–50	Itchy, linear wheals with a surrounding bright-red flare at sites of scratching or rubbing	No	Light stroking of skin causes an immediate wheal with itching
Cold urticaria	10–40	Itchy pale or red swelling at sites of contact with cold surfaces or fluids	Yes	10-min application of an ice pack causes a wheal within 5 min following removal of ice
Pressure urticaria	20–50	Large, painful or itchy red swelling at sites of pressure (soles, palms, or waist), lasting ≥ 24 h	No	Application of pressure perpendicular to skin produces persistent red swelling after a latent period of 1–4 h
Solar urticaria	20–50	Itchy pale or red swelling at site of exposure to ultraviolet or visible light	Yes	Irradiation by a 2.5-kW solar simulator for 30–120 s causes wheals in 30 min
Cholinergic urticaria	10–50	Itchy, monomorphic pale or pink wheals on trunk, neck, and limbs	Yes	Exercise or a hot shower elicits an eruption

Table 2
Chronic urticaria versus urticarial vasculitis

Feature	Chronic urticaria	Urticarial vasculitis
Characteristics of wheals		
Duration (h)	<24	>24
Purpura ^a	–	+
Pain	–	+
Itch	+	±
Hyperpigmentation	–	+
Systemic signs		
Arthralgia	±	+
Fever ^a	–	+
Abdominal pain	±	+
Nephritis ^a	–	+
Obstructive airways disease	–	+
Laboratory findings		
Elevated erythrocyte sedimentation rate	±	+
Increased acute-phase proteins	±	+
Reduced serum C3 ^a	–	±
Serum immune complexes ^a	–	±
Histologic features of skin		
Venular endothelial cell swelling	±	+
Leukocyte invasion of venular endothelium	±	+
Extravasation of red cells ^a	–	+
Leukocytoclasia ^{a,b}	–	+
Fibrin deposition	±	+
Findings on direct immunofluorescence		
C3	–	+
Immunoglobulin	±	+
Fibrin	±	+
Response to treatment with antihistamines	+	±

^a Major diagnostic criteria for urticarial vasculitis.

^b Defined as fragmentation of nuclei of neutrophil polymorphonuclear leukocytes.

plaques [4]. They can be found anywhere on the skin, including the scalp, palms, and soles [4]. Following their acute appearance, the wheals fade and leave no permanent mark on the skin. For many patients, the wheals are intensely itchy (especially at night) and are relieved by rubbing the skin, but not by scratching [4]. The intensity of the itch, however, is highly variable among patients. Differing from urticarial vasculitis, CIU is not associated with pain, purpura, or hyperpigmentation (Table 2) [1].

Approximately 50% of patients with chronic urticaria have concomitant oral and facial angioedema [1,4,5]. Angioedema is typically characterized either as short-lived, deep, dermal, and subcutaneous, or as submucosal edema; it commonly is limited to the tongue, eyelids, or lips [4,5]. Similar to wheals, angioedema usually resolves within 24 h. Unlike the wheals associated with urticaria, angioedema is associated with little or no pruritus [4]. Although it is uncommon, angioedema may sometimes affect the oropharynx, causing patients to experience difficulty in breathing; this complication can be life threatening.

Although the symptoms of CIU are primarily restricted to skin [4], fatigue is the symptom most frequently reported during episodic relapses. Gastrointestinal symptoms are occasionally reported in patients experiencing severe attacks; respiratory and arthralgic symptoms are rarely reported.

The frequency of attacks, the average duration of an episode of urticaria, and the total duration of disease are variable. Patients with urticaria without angioedema tend to have less frequent attacks of longer duration compared with patients who have urticaria with angioedema [5]. In general, the average duration of CIU in adults is 3–5 years, although it often persists for longer than 10 years [4].



Fig. 1. Photo of a patient with chronic idiopathic urticaria.

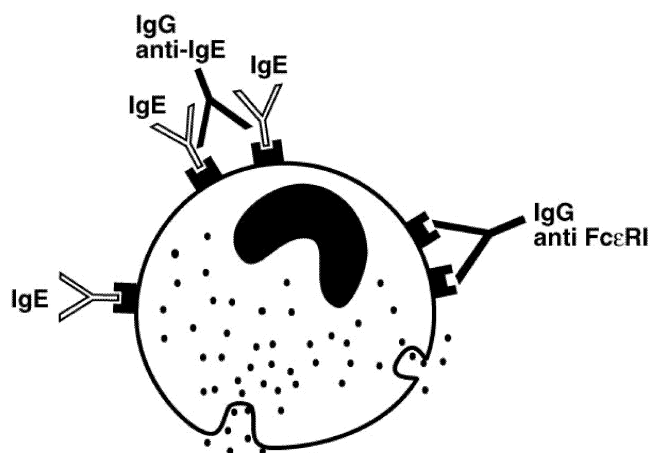


Fig. 2. Functional autoantibodies of chronic idiopathic urticaria. Cross-linking of IgE receptors can occur by binding of IgG antibodies to the IgE receptor or to IgE-bound antibodies. Crosslinking of IgE receptors triggers histamine and mediator release [4].

3. Pathophysiology

The mast cell appears to be the most important source of histamine in the skin and the primary effector cell in CIU [8]. Basophils are also involved in the pathogenesis of this condition, although the extent of their involvement remains to be elucidated [8]. Elevated levels of histamine have been found in the wheals of patients with different types of urticaria, especially during the early-phase reaction [9]. The specific allergen or antigenic stimulus responsible for degranulation and mediator release from mast cells or basophils is rarely identified in patients with CIU [2].

Potential stimuli that were thought to be involved, including *Helicobacter pylori*, intercurrent virus infection, food allergies, and aspirin, have been eliminated as possible triggers [4].

Evidence for the stimulation of mast cell or basophil degranulation and histamine release from wheals has only recently been demonstrated experimentally. In studies of patients with severe CIU, IgG autoantibodies directed against the α -chain of the high-affinity IgE receptor (Fc ϵ RI α) have been found in these patients [10,11]. These antibodies bind to and crosslink adjacent α -chains of Fc ϵ RI of the receptor, causing receptor activation and triggering histamine release from mast cells and basophils (Fig. 2) [4]. An additional 5% of the patients studied had evidence of functional anti-IgE autoantibodies [4]. These antibodies interact with IgE antibodies that are bound to the IgE receptor and, thus, also induce crosslinking of adjacent IgE receptors and release of histamines (Fig. 2) [4]. Overall, CIU may be explained by an autoimmune mechanism in 25–45% of patients [4].

When histamine is released, activation of histamine receptors on cutaneous blood vessels results in vasodilatation and increased vascular permeability; this leads to erythema and edema, respectively (Fig. 3) [2]. Although both H₁- and H₂-histamine receptors may be involved in the pathophysiology of urticaria, histamine-induced itching appears to be mediated by the H₁-receptors only [2].

Other mediators appear to play a role in regulating cell recruitment and promoting the development of urticarial wheals [2]. Mast cell mediators implicated in the pathogenesis of CIU include prostaglandin, leukotriene, proteases, and proteoglycans [2]. Specifically, prostaglandin

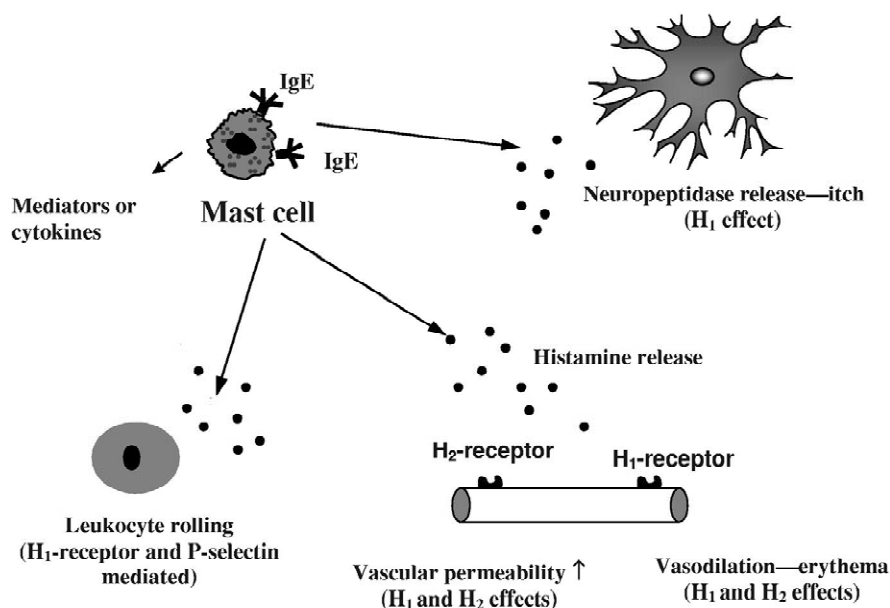


Fig. 3. Role of histamine in pathophysiology of urticaria. Mast cells are triggered to release histamine and other mediators after activation of IgE receptors. Histamine binds to H₁ and H₂ receptors on the vascular endothelium, causing vasodilatation and increased vascular permeability. H₁-receptors are also involved in flare through axon reflex (release of neuropeptidase) and leukocyte rolling (slowing of leukocytes before adhesion/tissue infiltration).

D₂ (PGD₂) and leukotriene C₄ (LTC₄) are known to increase vascular permeability; tumor necrosis factor, LTC₄, and interleukin-4 (IL-4) can promote cellular adhesion; IL-8 can stimulate neutrophil accumulation. Of these factors, IL-4 has been shown to be elevated in patients with CIU [12]. Although basophils express high-affinity IgE receptors and release LTC₄ [2], the role they play in the pathogenesis of CIU and their contribution to the wheal and flare reaction remain uncertain.

4. Treatment strategies and considerations: overview

4.1. General approach

For patients with CIU (i.e. those with no known antigenic stimulus), treatment is directed at eliminating or at least substantially reducing symptoms. General management of all patients should include a discussion of substances that should be avoided in order to minimize the likelihood or intensity of the episodes. For example, excessive alcohol consumption, overheated environments, and medications with nonspecific mast cell-releasing effects (e.g. aspirin and other nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors) should be avoided [1,4]. All patients should be advised to get enough sleep and to avoid overfatigue. Another routine recommendation is the avoidance of tight clothes because friction may enhance an attack. Overly restrictive diets have not proved to be beneficial [4]. Frequent tepid showers and topical application of an antipruritic cream may also comfort some patients during relapses. In patients with oropharyngeal edema, use of a spray solution of ephedrine may alleviate discomfort [1].

4.2. Pharmacologic interventions

Over the years, a variety of topical and systemic agents have been prescribed to treat patients with frequent outbreaks of wheals and pruritus. At one time, mast cell degranulation inhibitors, such as calcium channel antagonists (e.g. nifedipine) or β_2 -adrenergic antagonists (e.g. terbutaline), were suggested as adjunct therapy for refractory cases of urticaria. Experience with these drugs was not encouraging; therefore, they no longer have a role in treatment [1]. In addition, topical corticosteroids, topical antihistamines, and local anesthetics provide little benefit and should not be used [1].

For the past 5 decades, the value of administering systemic antihistamines to reduce the symptoms associated with CIU has been recognized [13]. The usefulness of the first-generation antihistamines (e.g. chlorpheniramine, diphenhydramine, promethazine) was limited by bothersome central nervous system (CNS) effects (e.g. sedation, impaired mental performance, and reduced cognitive function) and anticholinergic events (e.g. dry mouth). In

addition, interpatient variability or tolerance to a specific agent after prolonged treatment may limit the use of these antihistamines.

The 1980s were marked by the introduction of the second-generation antihistamines. These agents were developed in an attempt to improve on the adverse event profile of the earlier medications, particularly their sedative properties [13]. As a group, second-generation antihistamines are associated with decreased penetration of the blood–brain barrier [13], although some (e.g. cetirizine, levocetirizine) are still associated with sedation. Some of the early second-generation antihistamines (e.g. terfenadine, astemizole) were associated with cardiotoxicity and were removed from the US market secondary to life-threatening cardiac adverse events (e.g. QT_c interval prolongation and torsades de pointes) [14]. The potential for cardiotoxicity has been shown to be a drug-specific effect, and not a class effect of second-generation antihistamines.

Previously, first-generation antihistamines were the treatment of choice for patients with CIU; currently, second-generation and newly available antihistamines are the mainstay of therapy [15]. Because some of these agents (e.g. cetirizine, levocetirizine) are sedating, choice of an effective antihistamine requires careful clinical consideration [16]. In addition, some second-generation antihistamines (e.g. fexofenadine, ebastine) have other significant limitations, including the potential for drug–drug and drug–food interactions (Table 3) [16,17]. Desloratadine, the primary active metabolite of loratadine, is a potent, nonsedating H₁-receptor antagonist [18] that is a safe and effective once-daily treatment option for patients with CIU [19,20].

For very severe episodes of CIU that are recalcitrant to antihistamine therapy, a short course of systemic corticosteroids is sometimes recommended [1]. Although the prolonged use of steroids may cause systemic toxicity, their ability to rapidly reverse patients' symptoms may justify their use in certain circumstances [4].

5. Clinical considerations with antihistamines in the treatment of CIU

Because treatment of patients with CIU usually requires individual consideration, the goal of therapy is to find an agent that provides the desired clinical response for individual patients. It may be necessary to try several different agents before a satisfactory response is achieved. Patients must adhere to the prescribed regimen if the success of the chosen antihistamine is to be accurately determined; nonadherence is often associated with treatment failure [4]. The timing of antihistamine administration is also important. Although many patients achieve a satisfactory response with a once-daily morning dose of a nonsedating antihistamine, evening dosing with a sedating

Table 3

Advantages and disadvantages of second-generation and next-generation H₁-receptor antagonists for treatment of CIU

Drug (alphabetical)	Advantages	Disadvantages
Cetirizine	QD dosing; rapid onset; no known drug–drug interactions mediated by CYP-450 enzymes	Sedation and anticholinergic effects
Desloratadine	Same as loratadine. Additionally, provides 24-h relief; minimal anticholinergic effects; no known drug–drug interactions mediated by P450 enzymes or active drug transport systems; no QT _c interval prolongation	
Ebastine	QD dosing; nonsedating	Potential CYP-450 enzyme interactions
Fexofenadine	QD dosing; nonsedating; no known drug–drug interactions mediated by CYP-450 enzymes; no QT _c interval prolongation	Drug–drug interactions (i.e. ketoconazole/erythromycin) Reduced bioavailability with food
Levocetirizine	Same as cetirizine	Same as cetirizine
Loratadine	QD dosing; nonsedating; no clinically relevant drug–drug interactions mediated by P450 enzymes	
Mizolastine	No known drug–drug interactions mediated by CYP-450 enzymes	

QD, once-daily.

antihistamine may be appropriate for those patients whose symptoms are worse at night, unless the sedative properties continue into the next morning and interfere with activities during the day.

Selection of a specific antihistamine should be based on the following key properties: the antihistamine should have proven efficacy as demonstrated in controlled clinical trials by a high rate of symptom improvement (e.g. reduction in pruritus, diminished number or size of wheals) [13,21]. Optimally, the antihistamine selected should have a rapid onset of action, a durable (long-lasting) response, and anti-inflammatory properties. As with any medication, the selected antihistamine should have an excellent safety profile and a high degree of tolerability (i.e. no clinically relevant sedation, anticholinergic effects, or QT_c interval prolongation). Furthermore, the chosen agent should have a low potential for drug–drug and drug–food interactions. Because CIU is often associated with significant morbidity, the data from controlled clinical trials ideally should provide evidence that treatment has had a positive impact on patient quality of life (e.g. less fatigue, improved sleep, better ability to perform daily activities).

Many second-generation and newly available antihistamines can be used to treat patients with CIU. Currently available agents include desloratadine, loratadine, ebastine, mizolastine, cetirizine, levocetirizine, and fexofenadine. Although a review of the clinical profile of each agent is beyond the scope of this article, some important differences should be highlighted. As was mentioned previously, the histamine-induced wheal and flare model, which has been used traditionally to compare antihistaminic activities, has been shown to only mimic the early phase of a

true allergic reaction; it reflects virtually none of the inflammatory events of the late-phase response [22]. Thus, the efficacy of an antihistamine should be judged on its effectiveness in treating CIU in well-controlled trials and should not be decided on the basis of histamine-induced wheal and flare reactions alone.

Chronic idiopathic urticaria can be associated with substantial fatigue due to disturbed sleep; therefore, it is important to prescribe an antihistamine that does not cause sedation and further limit patients' abilities to perform normal daily tasks. Although most of the second-generation antihistamines are nonsedating, both cetirizine and its active enantiomer, levocetirizine, are associated with sedation [16]. These sedative effects are not circumvented by administration of an antihistamine in the evening; sedation may persist to the next day, causing daytime somnolence and impairing work performance.

Compared with terfenadine and astemizole, the newer antihistamines are safer, although the potential for drug–drug or drug–food interactions still exists with certain agents. Loratadine is metabolized by cytochrome P450 (CYP-450) enzymes in the liver; however, when it was coadministered with a macrolide antibiotic or an azole antifungal, no clinically relevant changes were assessed by electrocardiogram (ECG) analysis despite increases in loratadine plasma concentrations [23], and there was no evidence of cardiotoxicity [16]. Ebastine depends on CYP-450 enzymes for metabolism and is also subject to drug–drug interactions that affect its pharmacokinetic behavior [16]. Although ebastine has been shown in animal models to possess arrhythmogenic potential, the significance of these drug–drug interactions in clinical treatment has yet

to be determined [24,25]. The novel antihistamine desloratadine is metabolized through hydroxylation, primarily to 3-OH desloratadine. Cetirizine, mizolastine, and fexofenadine are not metabolized and are eliminated primarily as parent compounds [16].

Fexofenadine has been identified as a substrate of the P-glycoprotein (P-gp) and organic anion transport polypeptide (OATP) systems [26]. Certain drugs (e.g. azole antifungals, calcium channel blockers, erythromycin) inhibit these active transport systems, thereby affecting the plasma concentrations of P-gp or OATP substrates. When fexofenadine was coadministered with a known P-gp inhibitor—ketoconazole or erythromycin—the steady-state plasma concentrations of fexofenadine increased significantly [17,26]. On the other hand, grapefruit juice, apple juice, and orange juice, which are inhibitors of OATP, have been shown to decrease the bioavailability of fexofenadine [27,28].

In summary, the antihistamine selected for treatment of CIU should demonstrate a rapid and durable therapeutic response, have minimal anticholinergic adverse events, and have a very low potential to induce drug–drug or drug–food interactions; it should also be nonsedating. Use of an effective agent will lead to prolonged symptom control, thereby permitting patients to return to normal sleep patterns and to resume normal work and daily activities.

6. Desloratadine—a new treatment option for CIU

6.1. Efficacy

Desloratadine is a potent, new, nonsedating H_1 -receptor antagonist. The inhibitory effect of desloratadine on both CIU symptoms and the underlying pathophysiologic processes [15] has been demonstrated in recently available data from well-controlled clinical trials in patients with CIU [19].

Two multicenter, randomized, double-blind, placebo-controlled trials in adult patients with moderate-to-severe CIU have reported that once-daily desloratadine 5 mg improved both the symptoms of CIU and the quality of life of these patients [19,20].

In one study, desloratadine 5 mg significantly reduced the pruritus score in the desloratadine-treated group by the second day of treatment ($P<0.001$) (Fig. 4) [19,29], and this reduction was maintained during each week throughout the 6-week study period (each $P<0.001$) (Fig. 5) [19,30]. By week 6, desloratadine-treated patients experienced a 74% reduction in the severity of pruritus compared with a 48.7% reduction for patients administered placebo ($P<0.001$) [29]. Desloratadine significantly reduced the reflective average a.m./p.m. scores for the number and size of hives over the first 7 days (both $P<0.001$) and throughout the 6-week study period (all

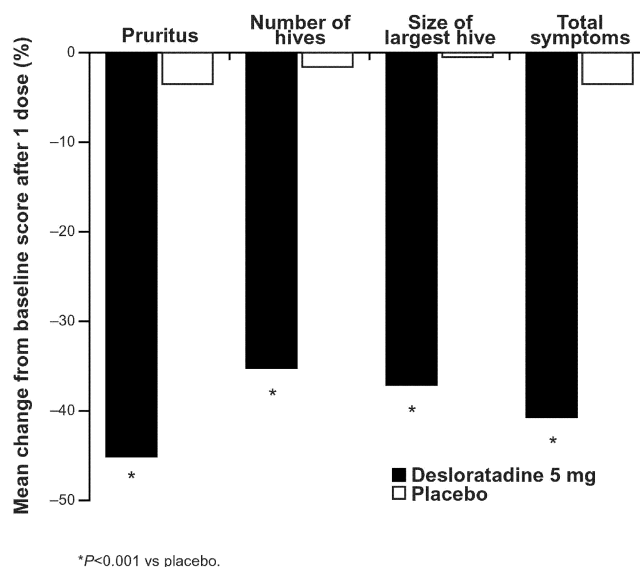


Fig. 4. Desloratadine has a rapid onset of action. By the second day of treatment, desloratadine 5 mg significantly reduced pruritus scores, number and size of hives, and total symptoms score (TSS) compared with placebo ($P<0.001$) [19,29].

$P=0.01$; Fig. 5) [19,30]. The average a.m./p.m. reflective total symptoms score (TSS) was improved following the first dose of desloratadine ($P<0.001$; Fig. 4) [19,29], and this improvement was maintained for each week of the study (each $P=0.002$; Fig. 5) [19,30]. In addition, desloratadine treatment significantly improved sleep quality ($P<0.05$) and the ability to perform daily activities ($P<0.001$). The rapid, durable activity of desloratadine and its ability to improve quality of life in patients with CIU are encouraging, especially for those patients with frequent attacks and prolonged episodes of CIU.

In a second study, desloratadine significantly reduced the pruritus score by day 2 ($P<0.001$) and reduced the average reflective a.m./p.m. pruritus score over the first week of treatment compared with placebo ($P<0.001$) [20]. The reduction in pruritus score was maintained throughout the end point week ($P=0.023$) and at the end point analysis ($P=0.004$) [20]. After 1 week of treatment, the reflective average a.m./p.m. scores for the number of hives and size of the largest hive were both significantly reduced in the desloratadine-treated group compared with the placebo group (both $P<0.05$). Improvement in TSS was apparent following the first dose of desloratadine 5 mg and, over the first 7 days, desloratadine significantly reduced the average a.m./p.m. reflective TSS compared with placebo ($P<0.001$). Sleep quality ($P=0.007$) and daily activity function ($P=0.001$) were also significantly improved in desloratadine-treated patients.

6.2. Safety

Preclinical studies with desloratadine provided initial

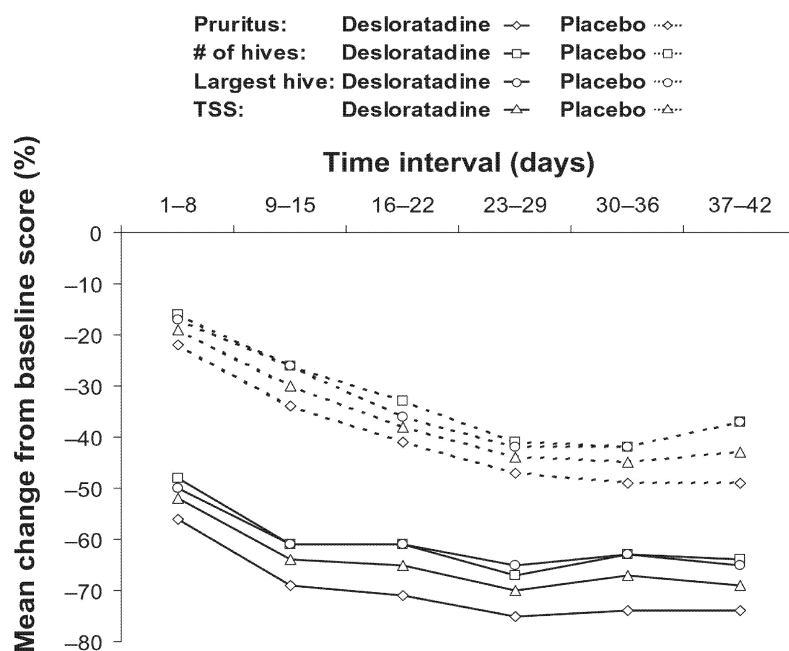


Fig. 5. Desloratadine has a prolonged duration of action. Over the first 7 days, desloratadine 5 mg significantly reduced the average reflective a.m./p.m. scores for pruritus symptoms, number and size of hives, and total symptoms score (TSS) ($P < 0.001$ for each parameter) compared with placebo; this reduction was maintained at each week throughout the 6-week study period ($P < 0.001$; $P \leq 0.01$; $P \leq 0.002$, respectively) [19,30].

evidence that it was associated with minimal CNS and cardiovascular effects [31]. Studies in mice and rats did not detect any significant behavioral, neurologic, or autonomic effects [31]. Administration of very high doses of desloratadine to rats, guinea pigs, and monkeys revealed no negative effects on blood pressure, heart rate, or ECG data [31]. QT_c interval lengthening was not observed in any of the animals tested.

Based on published Phase I to Phase III trial data, desloratadine has been shown to have an excellent safety and tolerability profile. Unlike some second-generation antihistamines, desloratadine is nonsedating, is not associated with substantial anticholinergic adverse events, and has been shown not to induce clinically relevant QT_c interval prolongation [20,32,33]. No clinically relevant cardiovascular events were reported when desloratadine was given to healthy men and women at up to nine times the clinical dose [33], and in clinical trials, desloratadine has been shown to have a safety profile similar to placebo [19].

6.3. Drug–drug interactions

Desloratadine has a low potential for drug–drug interactions with agents that interact with the CYP-450 metabolic system, specifically P-gp, or OATP. At steady state, coadministration of ketoconazole resulted in no significant

change in the extent or overall bioavailability of desloratadine [32]. The bioavailability of desloratadine was only slightly increased (1.1-fold) following concomitant administration of erythromycin compared with desloratadine alone [34]. Minimal changes (5%) in the bioavailability of desloratadine were observed with coadministration of azithromycin; in contrast, the bioavailability of fexofenadine was increased by 67% [35]. This study demonstrates the lower pharmacokinetic drug–drug interaction potential of desloratadine compared with fexofenadine.

After a single oral dose of either desloratadine or fexofenadine taken with grapefruit juice, the rate and extent of absorption of desloratadine were unaffected; in contrast, the bioavailability of fexofenadine was reduced by 30% [28]. Two separate single-dose studies have demonstrated that the bioavailability of desloratadine is unaffected by food [36]. Following both fasted conditions and a high-calorie, high-fat meal, the rate and extent of absorption of desloratadine remained unaltered. The clinical significance of these findings for fexofenadine has not been determined.

Collectively, these data show that drug–drug and drug–food interactions are not seen with desloratadine. It is anticipated that desloratadine will elicit predictable plasma concentrations when administered with a number of commonly prescribed drugs that interact with the CYP-450 metabolic system and active drug transporters.

7. Conclusions

CIU is a debilitating and common skin disorder with an unknown etiology. The condition is associated with long-term morbidity and suffering. The main symptom of CIU is pruritus and wheal formation, which is mediated primarily by histamine release, although other chemical mediators such as cytokines may also play an important role. The goals of therapy are to promptly reduce the extent and severity of symptoms while improving patients' quality of life. Because the disease is associated with frequent relapses and often persists for longer than 10 years, optimal therapy should provide long-term benefits.

Second-generation and newly available nonsedating antihistamines are now the preferred first-line treatment for CIU because they are highly effective and have a better tolerability profile than first-generation agents, such as diphenhydramine. Selection of the optimal antihistamine must be individualized to patients and should be based on proven clinical efficacy and the absence of sedation and other adverse effects. Importantly, the efficacy of an antihistamine should not be judged based on the histamine-induced wheal and flare model (low correlation with clinical outcome), but rather on its efficacy of treatment of CIU symptoms in well-designed clinical trials.

Desloratadine, a new, nonsedating antihistamine, is a potent antagonist of H_1 -receptors that has inhibitory effects on the mediators of allergic inflammation. Two placebo-controlled clinical trials have shown that 5 mg of desloratadine daily provides rapid and prolonged relief of symptoms in patients with moderate-to-severe CIU. Improvement in quality of life (e.g. less interference with sleep, improved performance of daily activities) has also been demonstrated with desloratadine. Desloratadine is safe and well tolerated (i.e. absence of CNS or cardiovascular adverse events and of QT_c interval prolongation) and has a low potential for drug–drug interactions. In summary, desloratadine provides many advantages over second-generation antihistamines currently available and represents a significant addition to the armamentarium for the treatment of CIU.

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