

Chronic urticaria: impact of allergic inflammation

Urticaria is defined by weals (hives), with or without angioedema, that appear and peak in minutes to hours, usually disappear within 24 h, and are accompanied by pruritus that worsens during the night. Urticaria is caused by cutaneous mast cell degranulation, attributed to immunological, nonimmunological, and idiopathic causes. Chronic idiopathic urticaria (CIU) is the diagnosis when the pathophysiological mechanism of persistent urticaria remains unclear; up to half of patients with CIU have functional autoantibodies directed against the high-affinity receptor for IgE (*FcεRI*) or against IgE itself, which appear to induce mast cell degranulation. Systemic histamine H_1 -receptor antagonists, such as desloratadine, are central to the management of CIU. The efficacy and safety of desloratadine, 5 mg once daily, was studied in a double-blind, randomized, placebo-controlled, multicentre trial that included 190 patients, ages 12 and above, with at least a 6-week history of CIU and experiencing a flare of at least moderate severity. Desloratadine was superior to placebo in controlling pruritus and total symptoms after the first dose, and its superiority was maintained throughout the full 6 weeks of the study. Measures of sleep, daily activity, therapeutic response, and global CIU status were also significantly improved with desloratadine after the first dose and maintained throughout the study.

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The weals (hives) of urticaria, with or without angioedema, appear and peak in minutes to hours and usually disappear within 24 h; the accompanying pruritus worsens during the night (1). Persistent urticaria, for which a clearly defined pathophysiological mechanism cannot be identified, is termed chronic idiopathic urticaria (CIU). Urticaria is one of the most common dermatological conditions, occurring most frequently in children and adolescents (prevalence 2.0–6.7%) and in atopic persons (prevalence 3–35%) (1).

Chronic urticaria negatively impacts quality of life via sleep disruption, fatigue, social isolation, energy loss, and emotional/sexual difficulties (2). The quality-of-life impact in patients with CIU is comparable to that seen in outpatients with psoriasis and in those with severe coronary heart disease (2,3). The impact for patients with concurrent physical urticaria is comparable to that seen in those with severe atopic dermatitis (3).

Systemic histamine H_1 -receptor antagonists, particularly those that are non-sedating, are central to the management of CIU and can improve both symptoms and quality of life (4,5). Desloratadine is a new, selective, histamine H_1 -receptor antagonist. It has a favourable pharmacokinetic profile that includes rapid absorption, bioavailability unaffected

by food or juice, a half-life of 21–27 h, and no significant drug–drug interactions (6). The overall adverse-event profile of desloratadine is similar to that of placebo, and no serious adverse events were reported among almost 2000 patients with seasonal allergic rhinitis who were administered daily doses of 5 mg in controlled clinical studies (6).

As reviewed elsewhere in this Supplement, *in vitro* studies have shown that desloratadine has high binding affinity for the histamine H_1 -receptor. It also inhibits the release or generation of many other inflammatory mediators by mast cells, basophils, and other cells involved in the allergy cascade (7). These inflammatory mediators include leukotriene C_4 , prostaglandin D_2 , tryptase, RANTES (regulated on activation, normal T cell expressed and secreted) induced by tumour necrosis factor- α (TNF- α), P-selectin, and intercellular adhesion molecule-1 (ICAM-1) induced by histamine, several interleukins (IL-1 β , IL-4, IL-5, IL-6, IL-8, IL-13, IL-18), and platelet-activating factor. In cultured human keratinocytes, desloratadine in high concentration (10^{-5} μ M) markedly inhibits the ability of interferon- γ (IFN- γ) to induce 1) expression of membrane ICAM-1, human leukocyte antigen-DR (HLA-DR), and up-regulation of major histocompatibility complex (MHC) class I, and 2) release of

RANTES and IL-18 (8). In healthy volunteers, desloratadine 5 mg lowered the erythematous reaction of the skin to UVB light, confirming anti-inflammatory activity (9).

This article reviews the classification of urticaria and the pathophysiology and differential diagnosis of chronic urticaria. The use of histamine H₁-receptor antagonists in the management of CIU is discussed, including the results from a recently published multicentre clinical trial that assessed the efficacy and safety of desloratadine.

Clinical classification of urticaria

There are several ways to classify urticaria in order to direct clinical management. Classification according to the kinetics of the lesions is the most common method employed, but classification according to the aetiopathophysiology of the lesions is more informative (Table 1) (1). Accurate diagnosis requires classification by both systems.

Acute urticaria

Acute urticaria is defined as the presence of lesions for less than 6 weeks. Acute urticaria, with or without angioedema, is the most common manifestation

Table 1 Clinical classification of urticaria based on kinetics and aetiopathophysiology

Classification scheme	Categories	Details
Kinetics	Acute	<6 weeks
	Chronic	>6 weeks
	Episodic	Intermittent
Aetiopathophysiology	Allergic	Urticaria occurs at some time in 20–30% of patients with chronic allergic diseases
	Focus reaction	Consequent upon a localized chronic infection
	Idiopathic	No identifiable cause, although up to one-third of patients have thyroid autoantibodies and up to half have autoantibodies to IgE and/or IgE-receptor
	Irritative–toxic	For example, after contact with nettles
	Physical	Cholinergic, pressure, solar, cold, heat, aquagenic
	Pseudoallergic	History of reaction to a certain substance, with no evidence for IgE antibodies
	Psychosocial	Conflict situation amplifies the urticarial symptoms
	Urticarial vasculitis*	Skin biopsy shows deposits of immune complexes
	Enzyme defects*	Hereditary angioedema, an autosomal dominant disease that afflicts one in 10 000–150 000 persons
	Mastocytosis*	Characterized by an abnormal increase of mast cells in tissues, most frequently the skin

*Rare.



Figure 1 Acute urticaria (drug-induced).

of allergy or intolerance to food and food additives, occurring in 40–60% of persons with IgE-mediated food allergy (10). The occurrence of acute urticaria during drug treatment is relatively common, occurs within 24 h of ingestion, and is often caused by penicillin, sulphonamides, and non-steroidal anti-inflammatory drugs (Fig. 1) (11,12). It is important to determine if drug-induced urticaria is allergic or pseudoallergic in origin; the former is potentially fatal, while the latter is rarely life-threatening (12).

Chronic urticaria

Persistence of urticaria beyond 6 weeks is defined as chronic urticaria (Fig. 2). The aetiopathophysiology of chronic urticaria is more difficult to determine than that of acute urticaria.

Physical urticaria is one of the most common aetiopathophysiologicals of chronic urticaria (13). It is characterized by wealing and itching that develop promptly after the appropriate physical challenge



Figure 2 Chronic urticaria.

and lasts only a few hours. An exception is delayed pressure urticaria, in which weals develop 2–6 h after challenge and last for more than 24 h (14). Unlike the other physical urticarias, delayed pressure urticaria responds poorly to histamine H_1 -receptor antagonists; severely afflicted patients may need large doses of systemic glucocorticosteroids to control symptoms (14). The most frequent precipitating causes of physical urticaria are pressure (dermographism and delayed pressure urticaria) and heat or exercise (cholinergic urticaria); others include light (solar urticaria), cold, and water (aquagenic urticaria) (13–16).

Contact urticaria is another common type of chronic urticaria. Contact urticaria may be either nonallergic (e.g. pseudoallergic or irritative–toxic) or allergic in nature. Nonallergic agents of contact urticaria are widespread as ingredients in food, cosmetics, and medications (17). Allergic contact urticaria is a manifestation of immediate-type hypersensitivity, occurs most commonly in atopic individuals, and is mediated primarily by histamine; natural rubber latex is one of the most important causes of allergic contact urticaria (17). The management of contact urticaria is predicated upon avoidance of the precipitating agent.

Some rare causes of chronic urticaria include urticarial vasculitis, hereditary angioedema, and mastocytosis. Weals that persist for longer than 24 h and leave residual pigmented changes in the skin may indicate the presence of immune complex deposits; these deposits signify urticarial vasculitis, a marker for underlying autoimmune disease, such as systemic lupus erythematosus (1). Hereditary angioedema is a rare autosomal dominant disease caused by a defect of the C1 esterase inhibitor enzyme (1). It manifests as recurrent attacks of intense, massive, localized oedema without concomitant pruritus (18). Mastocytosis includes “a heterogeneous group of disorders characterized by abnormal growth and accumulation of mast cells” (19). Mastocytosis may manifest dermally or systemically; urticaria pigmentosa is the most common type of cutaneous mastocytosis. Unlike most other chronic urticarias, these rare causes of chronic urticaria do not respond well to histamine H_1 -receptor antagonists.

In the absence of an identifiable aetiopathophysiology, chronic urticaria is termed idiopathic (CIU). The urticarial wheals of CIU last longer than those of physical urticaria – at least 8–12 h – and itching is almost always severe, especially in the evening and nighttime (14). Angioedema occurs concurrently with CIU in about 50% of cases (20). Markers of autoimmunity may be found in a significant proportion of patients with CIU (21). A commonly encountered marker of autoimmunity,

histamine-releasing IgG autoantibodies against the high-affinity receptor for IgE ($Fc\epsilon RI$), or against IgE itself, occurs in 25–45% of patients with CIU (14). These patients have significantly more weals, a wider distribution of weals, more itching and systemic symptoms, and lower serum IgE levels than patients without $Fc\epsilon RI$ /IgE autoantibodies (22). Also, skin biopsies of patients with $Fc\epsilon RI$ /IgE autoantibodies often exhibit evidence of infiltrates in which perivascular polymorphonuclear cells (i.e. neutrophils, scattered eosinophils, and mononuclear cells) predominate (23). Thyroid autoimmunity occurs in up to one-third of patients, mostly in the absence of clinically apparent thyroid disease or altered serum thyroid-stimulating hormone levels (21,24,25). In such people symptoms of urticaria usually respond to levothyroxine sodium therapy (24).

Intermittent urticaria

Although CIU is by definition chronic, with daily or almost daily symptoms, intermittent symptoms are also common. In intermittent idiopathic urticaria, symptoms occur in bouts that last for days or weeks, with intervals of days, weeks, or months in between (14).

Pathophysiology of chronic urticaria

Urticaria is caused by degranulation of cutaneous mast cells and/or basophils (1). Degranulation releases potent vasoactive mediators that induce vasodilatation, which results in erythema. Vasoactive mediators also increase the permeability of capillaries and small veins, which results in weal formation. The itching and pain are caused by consequent sensory nerve stimulation. The main vasoactive mediator is histamine, but others may include arachidonic acid metabolites, leukotrienes, prostaglandins, serotonin, acetylcholine, platelet-activating factor, heparin, kinin, and neuromediators released from cutaneous nerve endings (1).

Degranulation is attributed to immunological (autoimmune, IgE-dependent, immune complex, complement-dependent), nonimmunological (direct mast cell-releasing, pseudoallergens such as drugs), and idiopathic causes. Urticarial vasculitis is thought to be caused by immune complex-mediated inflammation (26). Hereditary angioedema is caused by complement-mediated mechanisms (26). One of the most important mechanisms inducing mast cell degranulation in chronic urticaria is the presence of histamine-releasing IgG autoantibodies against $Fc\epsilon RI$ /IgE, which has been demonstrated in 25–45% of patients with CIU (Fig. 3) (14). Immunoreactive (nonhistamine-releasing) autoantibodies against

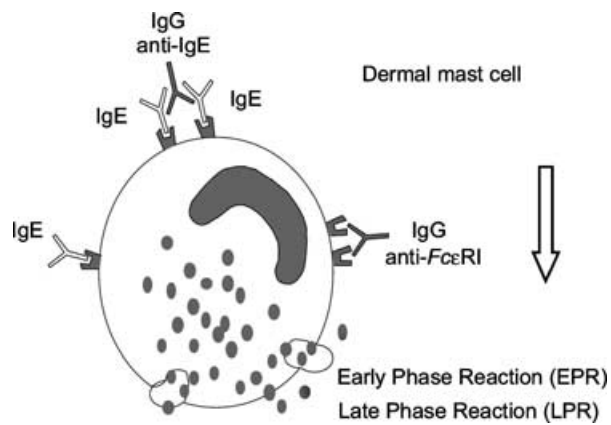


Figure 3 Functional autoantibodies in chronic idiopathic urticaria. IgG-anti-IgE antibodies combine with and cross-link adjacent receptor-bound IgE. IgG-anti-FcεRI antibodies combine with and cross-link adjacent α-chains of FcεRI. The grey notched membrane structures represent α-chains of FcεRI expressed on the surface of a dermal mast cell. Reproduced with permission from (14).

FcεRI have been found in serum of patients with physical urticarias (14).

Differential diagnosis of chronic urticaria

Distinguishing physical urticaria and contact urticaria is an essential first step in the differential diagnosis. This limits the investigation to elimination and/or challenge testing with, for example, suspected physical factors, allergens, drugs, and dietary pseudoallergens. In addition to a careful allergy-relevant history and a physical examination, standard diagnostic laboratory tests, such as complete blood count (CBC) and erythrocyte sedimentation rate (ESR), and total serum IgE levels are used as a screening approach during the basic investigation.

During the basic investigation phase, the patient is treated symptomatically for up to 4 weeks. Many cases of urticaria will resolve spontaneously, or in response to elimination of a causative factor. If the condition persists, more intensive investigation is indicated. This includes a detailed dietary history, tests for food and drug allergies, and examination for occult infection, malignancy, and underlying systemic disease. Diagnostic measures during this phase of the investigation may include testing for *Helicobacter pylori* infection, gastroscopy, stool culture for parasites, and an antinuclear antibody (ANA) panel. Additional investigations may include an elimination diet, food challenge and provocation diet, oral provocation tests for idiosyncrasy with food additives, and measurement of serum complement level.

Testing for autoantibodies may be warranted. Evaluation of thyroid function and the presence

of autoimmune thyroid disorders (i.e. antithyroid peroxidase/antithyroglobulin antibodies) are valuable, particularly in people with symptoms of hypothyroidism. Intracutaneous skin testing with autologous serum may induce a weal-and-flare reaction that suggests autoantibodies to FcεRI/IgE (20).

Skin biopsy may be necessary when a diagnosis remains elusive. Urticarial vasculitis is confirmed by histopathological evidence of leukocytoclastic vasculitis in a suspect skin lesion (27,28). The dermographism of urticaria pigmentosa (cutaneous mastocytosis) can be differentiated from the dermographism of physical urticaria by the increased number of skin mast cells in the former (14).

Treatment of chronic idiopathic urticaria

Nonsedating histamine H₁-receptor antagonists

The central role of nonsedating histamine H₁-receptor antagonists in the therapy of CIU is supported by the conclusions of evidence-based review (29), consensus report (5), and practice guidelines (26). Maximum benefit is obtained from regular daily administration, rather than “as required” dosing (14). Nonsedating histamine H₁-receptor antagonists include piperidines (astemizole, desloratadine, and loratadine) and butyrophenones (fexofenadine, terfenadine). Cetirizine, a piperazine, is considered mildly sedating (30).

The efficacy and safety of desloratadine 5 mg once daily were studied in a double-blind, randomized, placebo-controlled, multicentre trial (31). The study enrolled 190 patients, aged 12 and above, with at least a 6-week history of CIU and experiencing a flare of at least moderate severity. Patients scored symptoms – pruritus, number of hives, and size of the largest hive – on 4-point scales each morning and evening, both as experienced at the time of assessment (instantaneous) and during the previous 12 h (reflective). A total symptom score (TSS) was calculated from the sum of these individual symptom scores. Patients also scored interference with sleep and daily activities.

Desloratadine was superior to placebo on the basis of the primary efficacy variable; the mean change from baseline in the morning and evening reflective pruritus symptom score over the first 7 days of treatment was reduced by 56.0%, compared with a 21.5% reduction in placebo-treated patients ($P < 0.001$). Desloratadine was superior to placebo in controlling pruritus beginning with the first dose and maintained this superiority throughout the full 6 weeks of the study (Fig. 4). Similar results were obtained for total symptoms. Measures of sleep (Fig. 5), daily activity (Fig. 6),

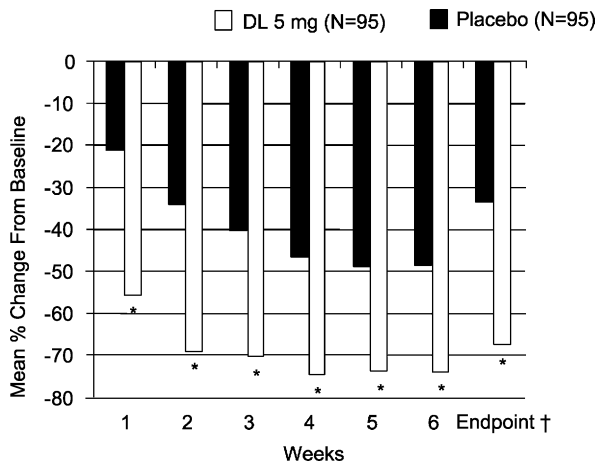


Figure 4 Mean change from baseline in morning/evening reflective pruritus score. * $P < 0.001$. †Last available week's average. Adapted from (31).

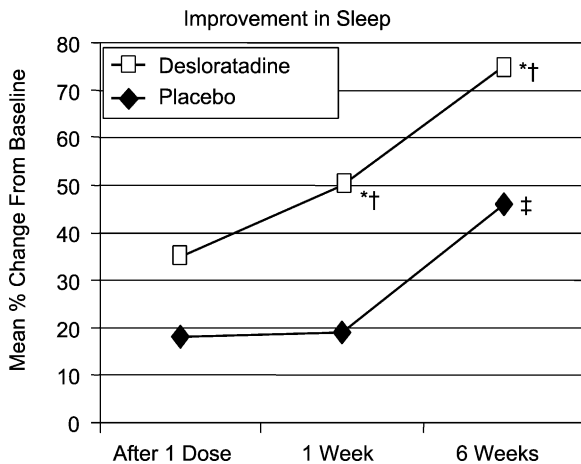


Figure 5 Efficacy in chronic idiopathic urticaria (CIU). Desloratadine reduced CIU-induced sleep disturbance. * $P < 0.001$ for change from baseline. † $P < 0.05$ for change from baseline. ‡ $P < 0.05$ for change from baseline. Adapted from (31).

therapeutic response, and global CIU status were also significantly better with desloratadine after the first dose and maintained throughout the study. No significant adverse events occurred.

Other medications

Patients with difficult-to-control pruritus at night have been treated classically with a bedtime dose of a sedating H_1 -receptor antagonist (e.g. doxylamine, dimetinden, pheniramine, clemastine, promethazine, alimemazine, cyproheptadine, and ketotifen). However, residual daytime sedation may be a problem that could negatively affect performance of

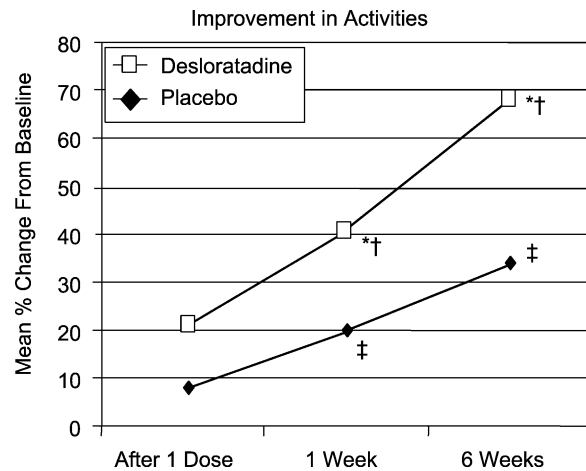


Figure 6 Efficacy in chronic idiopathic urticaria (CIU). Desloratadine reduces interference with daily activities. * $P < 0.001$ for change from baseline. † $P < 0.05$ for between-group difference. ‡ $P < 0.05$ for change from baseline. Adapted from (31).

daily activities. As noted above, desloratadine therapy improved measures of both sleep and performance of daily activities via control of symptoms.

Histamine H_2 -receptors may be involved, along with H_1 -receptors, in producing the increased vascular permeability (32,33) and/or pruritus (34) that results from histamine release in the skin. Addition of a histamine H_2 -receptor antagonist has been shown to provide statistically significant benefit in the management of CIU in controlled clinical studies, although the clinical significance of the benefit remains unknown (14).

Glucocorticoids are not generally recommended for the treatment of CIU but may be useful in patients with autoantibodies to $Fc\epsilon RI/IgE$ and severe symptoms. Cyclosporin (35) and intravenous immunoglobulin therapy (36) are also of value in this subgroup of patients. Other medications that may be useful in recalcitrant cases of CIU include mast cell degranulation inhibitors (i.e. oral β -adrenergic agonists such as terbutaline or albuterol) and leukotriene antagonists.

Conclusions

CIU decreases quality of life significantly. Hence, the aim of treatment is to provide rapid and sustained symptomatic relief. Nonsedating H_1 -receptor antagonists are the primary treatment modality. Desloratadine, a new, selective, nonsedating H_1 -receptor antagonist, provides rapid and enduring relief of pruritus, reduces the number and size of hives, reduces pruritus-related sleep disturbance, and improves activities of daily living.

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