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Desloratadine in the treatment of chronic idiopathic urticaria

Chronic idiopathic urticaria (CIU) is a common dermatologic disorder that may severely impair quality of life. Patients may suffer symptoms such as pruritus and disfigurement due to wheals for years or decades. Advances have been made in the last 10 years with the identification of an autoimmune pathogenesis in a significant proportion of patients. Despite this, treatment remains symptomatic, and antihistamines are the first choice of therapy once the diagnosis of CIU has been established. The goal of treatment is rapid, long-lasting symptom relief, and currently available antihistamines fail to provide this in many cases. Desloratadine is a novel, potent H_1-receptor antagonist with additional inhibitory effects on inflammatory mediators such as cytokines and adhesion molecules. Newly published data on the efficacy and safety of desloratadine in CIU is highly encouraging, suggesting that the drug may improve symptom control above that currently available.

J. Ring, R. Hein, A. Gauger
Division of Environmental Dermatology and Allergy
GSF TUM, Dermatologische Klinik, Technische Universität München, Munich, Germany

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Professor Johannes Ring
Dermatologische Klinik
Techniche Universität München
Biedersteinerstrasse
D-29802 München
Germany

Chronic idiopathic urticaria (CIU) is a common skin condition that affects 0.1–3% of people in the USA and Europe (1) and accounts for nearly 75% of all chronic urticaria cases (2). CIU is defined classically as the appearance of hives/wheals on most days for more than 6 weeks, in the absence of a causative physical or environmental trigger (3). Therefore, the diagnosis of CIU is mainly one of exclusion, and the clinical investigative process can be lengthy. Hematologic, biochemical, immunologic, and endocrine assays are needed to provide direct or indirect evidence of systemic allergic, inflammatory, infectious, or autoimmune processes that may cause chronic urticaria. Thereafter, sensitivity to foods, environmental agents/pollutants, and the presence of chronic infection or occult malignancy must all be excluded before a diagnosis of CIU can be finally established (4).

The duration of CIU varies greatly from patient to patient, with some individuals suffering irritating symptoms such as pruritus for decades. Patients with CIU have measurable decrements in quality of life, primarily due to recurrent itch, poor sleep, and the physically unappealing nature of the lesions. The activities of daily life and social life are badly affected by CIU. Indeed, the magnitude of this impairment of quality of life approximates that of chronic heart disease (5). Therefore, the goal of treatment in CIU is rapid and prolonged symptom control, thus allowing a return to normal sleep patterns and social activity.

Antihistamines have long been the mainstay of treatment for patients with CIU (6), and second-generation drugs have replaced older agents to a large extent for reasons of safety. However, the therapeutic response is not uniform across all patients, and improvements are continually sought with respect to pharmacologic potency and duration of action. Desloratadine (AERIUS™, Schering-Plough Corp.) is a new nonsedating H_1-receptor antagonist with the strongest peripheral H_1-blocking effects yet reported. Desloratadine also has a range of inhibitory effects on mediators and cytokines that play an important role in chronic allergic inflammation. These antiallergic and anti-inflammatory activities may translate into improved clinical responses in patients with CIU. This brief review assesses newly available clinical data on desloratadine in CIU and places it in the context of our current immunopathologic understanding of CIU.

Pathophysiology of CIU

The wheals of chronic urticaria have a characteristic appearance, namely, a pinkish-red center that merges into a red surround. These wheals are itchy and edematous and may coalesce to form giant wheals that are very uncomfortable and unsightly. In many cases, angioedema with infiltration and swelling at the lower dermal and submucosal levels accompanies chronic urticaria. Macroscopically, the wheals of CIU bear a striking resemblance to the cutaneous late-phase response (LPR) to allergen (7). Because of this similarity, many patients endure exhaustive investigations for causative dietary or household allergens. These physical similarities to the cutaneous LPR are also reflected at the microscopic level. Histologically, increased numbers of mast cells, T helper cells, and neutrophils can be identified. Cellular activation also occurs, with the release of large amounts of histamine

and other mediators e.g. tryptase, chymase, heparin, leukotrienes, prostaglandins, and platelet-aggregating factor in affected skin (8). Upregulation of adhesion molecules and cytokines can also be observed (9, 10). The result is perivascular leukocyte infiltration and tissue edema, although these structural changes are not associated with structural damage to the dermis. Indeed, apart from damage inflicted by scratching, CIU wheals resolve completely and spontaneously within a day or so.

Given the micro- and macroscopic similarities between CIU wheals and the cutaneous LPR to allergen, a great deal of research has focused on establishing the nature of the link. An important breakthrough was made in the early 1990s. It had been noted previously that autologous intradermal injection of serum from patients with CIU could cause wheals, pointing to a circulating factor that could activate cutaneous mast cells. Moreover, autoimmune thyroid disease was found to occur at a higher frequency in patients with CIU. Greaves' group in London identified an IgG autoantibody in the serum of patients with CIU that was specifically directed against the α-subunit of the high-affinity IgE receptor, FcεRI (11). This autoantibody was functional, in that it caused mast-cell activation and histamine release. These anti-FcεRI antibodies or distinct functional anti-IgE autoantibodies (12) can be identified in up to 45% of CIU patients. This implies that CIU may be predominantly an illness in which symptoms are produced by autoimmune targeting of the body's allergen defense system. Basophils, which also express FcεRI, are affected in CIU, and basophil numbers and immunologic reactivity are decreased in CIU (13), possibly via autoimmune mechanisms.

Despite this important advance, the pathogenesis of CIU remains uncertain in a significant proportion of cases. However, it is likely that mast cells may be activated by various inherited or conditioned immune and nonimmune events. Autoantibodies to other factors may degranulate mast cells via separate cell-surface receptors. The susceptibility of mast cells to degranulation by unknown serum factors and the magnitude of this response may be determined by genetically polymorphic molecular events.

Pharmacologic profile of desloratadine

Desloratadine is the active metabolite of loratadine, which itself has been widely used in CIU. Pharmacologically, desloratadine has a number of advantages over its parent compound, primarily in terms of novel anti-inflammatory activity and enhanced H_1-receptor blockade. Desloratadine binds avidly to human histamine H_1-receptors *in vitro;* indeed, it has the highest H_1-receptor affinity of all currently available antihistamines (15). The K_i for desloratadine was 0.87 nM, compared with 175 nM for fexofenadine and 138 nM for loratadine. This translates into relative potencies of 201, 3.7, 1.2, and 1.0 for desloratadine, cetirizine, loratadine, and fexofenadine, respectively (16). This receptor binding is selective, as desloratadine has a low affinity for both the H_2 and the muscarinic receptors (15, 17). Furthermore, desloratadine does not penetrate the blood–brain barrier in animal studies, a fact which has been confirmed by the lack of sedation or cognitive impairment in clinical trials (18–20).

Apart from its H_1-receptor inhibition, desloratadine also has novel antiallergic activity. *In vitro* experiments have demonstrated that desloratadine inhibits the release by mast cells and basophils not only of histamine (21), but also tryptase and the arachidonic acid products leukotriene C_4 and prostaglandin D_2 (22). These mediators are generated by mast cells in response to activation (by allergen and other agents), and are important in promoting local inflammation and cellular infiltration. It is now widely recognized that local mast-cell activation leads to widespread upregulation of inflammatory cytokines, chemokines, and adhesion molecules. The net result of this cascade of activity is the maturation, chemoattraction, accumulation, and activation of chronic allergic cells such as basophils and eosinophils, leading to late-phase local inflammation. Desloratadine has been shown to inhibit many of these important mediators, including the cytokines IL-4, IL-13, IL-6, TNF-α, and GM-CSF (23–25), the chemokines IL-8 and RANTES (26), and adhesion molecules such as P-selectin and ICAM-1 (27, 28). Furthermore, desloratadine reduces eosinophil chemotaxis and activation *in vitro* (29), although the effects on other chronic inflammatory cells and in the *in vivo* situation are less certain. However, it does appear that desloratadine has biologic activities that may translate into greater clinical efficacy in diseases such as CIU.

Clinical experience with desloratadine in CIU

A double-blind, placebo-controlled multicenter trial of desloratadine in moderate-to-severe CIU has recently been completed. This large study ($n = 190$) revealed important information on the efficacy, tolerability, and onset of action of desloratadine in patients with CIU. Patients with active CIU received 5 mg desloratadine or placebo daily for a maximum period of 6 weeks. The patients attended daily for the first 4 days and then weekly for 6 weeks or until discontinuation. Symptoms such as pruritus, the number of hives, and the size of the largest hive were scored twice daily, while interference with sleep was scored in the morning and interference with daily activities was scored only in the evening (all scored as 0 [none] to 3 [severe]). Composite scores of current and reflective (over the previous 12 h) symp-

toms were also assessed morning and evening, thus providing four scores per day. The primary efficacy parameter was the mean change from baseline in reflective pruritus score during the first 7 days of treatment. In the desloratadine group, pruritus scores fell by 56.0%, compared with 21.5% with placebo ($P<0.001$). Similar decreases with desloratadine were seen in secondary efficacy parameters such as number of hives (-48.4% *vs.* -15.8%; $P<0.001$), size of the largest hive (-49.7% *v.* -17.0%; $P<0.001$), and total symptom score (-51.6% *vs.* -19.3%; $P<0.001$). Desloratadine treatment also significantly improved sleep and activities of daily life in comparison with placebo. Over week 1 of treatment, interference with sleep fell by 53.0% and 18.4% ($P<0.001$) with desloratadine and placebo, respectively. Interference with daily activity mirrored this with falls of 50.2% and 20.0% ($P<0.001$) in patients receiving desloratadine and placebo, respectively.

When considered in isolation, these results over week 1 demonstrate admirable clinical efficacy with desloratadine in patients with active moderate-to-severe CIU. Further analyses over the entire length of the trial demonstrate the durability of desloratadine's clinical effects. With respect to pruritus, patients in the desloratadine group maintained a statistically significant improvement over placebo ($P<0.001$) to the end of the trial at week 6 (Fig. 1). Similarly, all other secondary efficacy parameters, including interference with sleep and daily activities, were significantly better in the desloratadine group than in the placebo group (Fig. 2a and b).

One of the primary aims of treatment in CIU is fast symptom relief. Close examination of the data from this trial revealed that desloratadine had a rapid onset of action. Assessments of all symptoms were made daily for the first 4 days of the study. After a single dose of medication, pruritus had fallen by 44.6% in the desloratadine group, compared with only 19.5% in those taking placebo ($P<0.001$). This rapid onset of action and prolonged duration of efficacy were mirrored in total symptom score, interference with sleep/daily activities, and hive size/number (Fig. 3).

Desloratadine was rated highly by both patients and investigators with respect to overall CIU improvement and therapeutic response during the trial. These joint investigator/subject assessments demonstrated the significant superiority of desloratadine over placebo at all

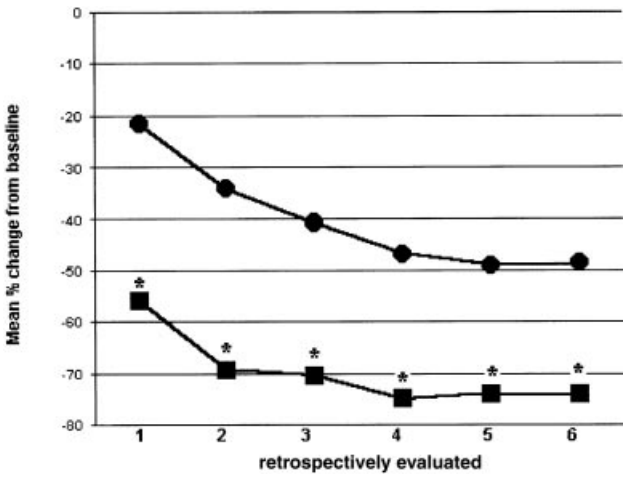

Figure 1. Subject-evaluated mean 12-h retrospectively evaluated pruritus score (primary efficacy parameter). Patients received either desloratadine 5 mg (n=95) or placebo (n=94) once daily. Symptom scores were rated from 0 (absent) to 3 (very severe). Desloratadine (squares), placebo (circles).
*$P<0.001$ *vs* placebo.

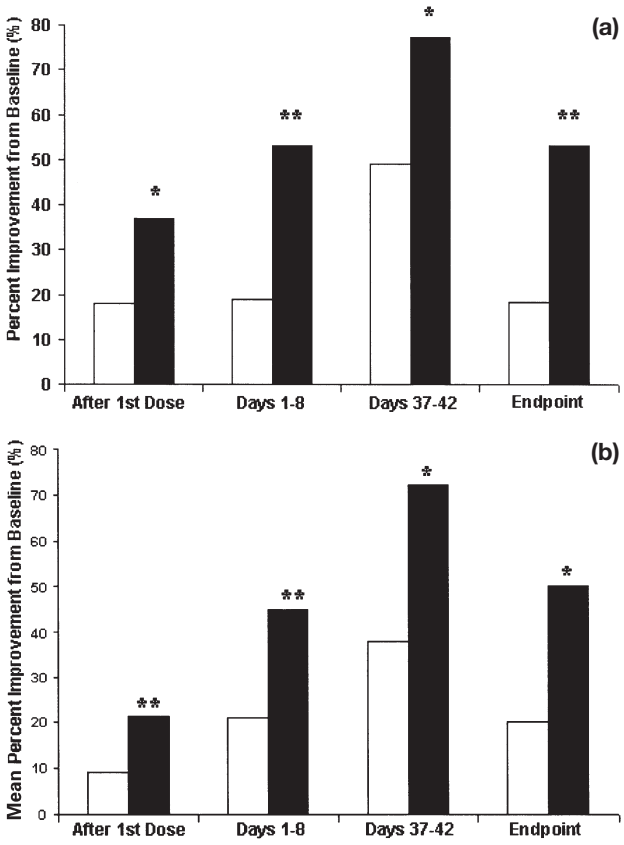

Figure 2a. Results of subject-evaluated AM prior 12-h interference with sleep analysis. Patients received either desloratadine 5 mg (filled column) or placebo (open column) once daily, and rated interference with sleep in morning before taking study medication. From first dose onward (i.e., rated day 2, AM), desloratadine provided significantly greater improvements in sleep scores than placebo. *$P<0.001$ *vs* placebo; **$P<0.05$ *vs* placebo.
Figure 2b. Results of subject-evaluated PM prior 12-h interference with daily activity results. Patients received either desloratadine 5 mg (filled column) or placebo (open column) once daily (AM) and rated interference with daily activities in evening. From first dose onward (i.e., rated day 1, PM), desloratadine provided significantly greater improvements in daily activity scores than placebo. *$P<0.001$ *vs* placebo; **$P=0.02$ *vs* placebo.

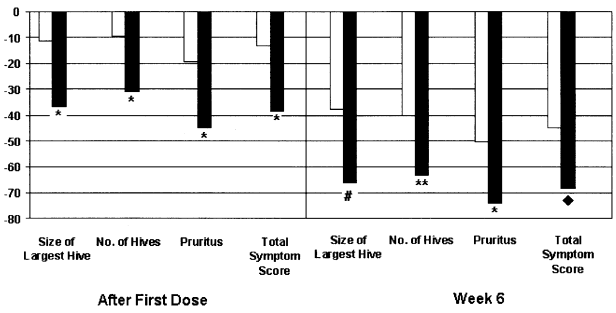

Figure 3. Rapid onset of action and prolonged duration of efficacy of desloratadine 5 mg in CIU. Results of hive number/size, pruritus score, and total symptom score are shown after first dose and at week 6 of trial. Desloratadine demonstrated significant effects on efficacy parameters from first dose, and effects lasted for full duration of trial. $*P<0.001$; $\#P=0.04$, $**P=0.02$; $\blacklozenge P=0.002$.

time points (days 4, 8, 15, 29, and 43) with respect to CIU condition ($P<0.001$) and therapeutic response ($P\leq 0.002$).

Desloratadine was safe and well tolerated during the trial. The most common adverse events in both groups were headache, viral infection, fatigue, and pharyngitis. Only one severe adverse event was considered to be related to desloratadine (headache in one patient); however, this subject continued in the trial. ECG, laboratory, and vital sign data were all similar in the desloratadine and placebo groups, and no clinically relevant changes were noted.

Conclusion

Our understanding of the pathophysiology of CIU has deepened over the past decade, with the identification of functional autoantibodies in a significant proportion of patients. However, the pathogenesis of CIU in more than 50% of cases remains unclear. As CIU can decrease quality of life significantly, the aim of treatment is to provide rapid and durable symptomatic relief. Despite the wide availability of nonsedating antihistamines, many patients continue to experience troublesome symptoms, sometimes for decades. This need may be met by desloratadine, a potent, nonsedating H_1-receptor antagonist with novel antiallergic and anti-inflammatory actions. Clinical experience in CIU has so far shown desloratadine to be a safe and effective treatment, providing rapid onset of action and long duration of symptom relief.

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