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Therapeutic points of intervention and clinical implications: role of desloratadine

Desloratadine, a potent, once-daily, orally active, nonsedating, histamine H_1-receptor antagonist, inhibits the release of histamine and other inflammatory mediators. Once-daily desloratadine therapy rapidly reduces the symptoms of perennial allergic rhinitis and seasonal allergic rhinitis (SAR), reduces the use of inhaled albuterol by patients with SAR and concomitant asthma, and improves symptoms and quality of life in patients with chronic idiopathic urticaria. An open-label, observational study in SAR patients revealed that desloratadine therapy significantly reduced nasal, ocular, dermal, asthma, and total symptoms, and enabled half of the patients with concomitant asthma to reduce their use of asthma medications. Globally, more than 91% of patients and physicians judged desloratadine to have excellent or good efficacy, and more than 98% judged it to have excellent or good tolerability. Furthermore, desloratadine therapy improved quality of life, decreasing by more than 10-fold the percentage of patients whose daily activities and/or sleep were moderately or severely affected by SAR. Allergic rhinitis, a major chronic airway disease that is a risk factor for asthma, warrants extended diagnostic procedures and well-tolerated therapy that encompasses the entire airway, addresses multiple steps in the allergic inflammatory cascade, and is effective on nasal, ocular, dermal, asthma, and total symptoms.

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The release of histamine and other proinflammatory mediators from mast cells is central to the early phase of an IgE-dependent allergic reaction and contributes to late and ongoing allergic inflammation (1). Histamine H_1-receptor antagonists (antihistamines) block histamine H_1-receptor activity. Most classical and newer antihistamines have additional antiallergic properties that differ depending on the molecule (2). The variability between antihistamines in H_1-receptor antagonist activity and antiallergic effects, possibly in combination with differences in lipophilicity and tissue deposition, result in different degrees of efficacy on skin, nose, eye, and lung symptoms (2).

Allergic rhinitis is the most prevalent manifestation of IgE-dependent allergy. It affects about 10% to 20% of the general population in many developed countries (3), and the prevalence has increased in some geographic areas in the last decades (4). Allergic rhinoconjunctivitis is common in children worldwide, with the 1-year prevalence across centres varying from 0.8% to 14.9% among children aged 6–7 years and from 1.4% to 39.7% among 13–14-year-old adolescents (5). As expressed in the European Academy of Allergology and Clinical Immunology (EAACI) consensus statement, allergic rhinitis is underestimated as a cause of suffering and impaired quality of life and may contribute to learning problems and sleep disturbances (3).

Desloratadine is a potent, once-daily, orally active, nonsedating H_1-receptor antagonist. This article reviews desloratadine preclinical and clinical allergy data. It details the multiple points of intervention of desloratadine in the allergy cascade and describes the utility of the medication in the treatment of allergic disease, focusing on seasonal allergic rhinitis (SAR), including the quality of life of patients with SAR.

Preclinical data

Desloratadine inhibits the release or generation of histamine and many other inflammatory mediators, resulting in a positive impact on early-phase reaction symptoms and chronic inflammation (Table 1).

Antihistaminic profile

The antihistaminic potency of desloratadine has been demonstrated by using the human H_1-receptor cloned and expressed in Chinese hamster ovary cells (Table 2). According to these data, desloratadine is one of the most potent antihistamines currently available, with a potency that is 80–115 times higher

Table 1 The allergic inflammatory cascade: desloratadine intervention points, actions, and theoretical consequences (*in vitro* data)

Cell population	Target (action)	Theoretical consequence
Mast cell and/or basophil	Histamine (↓ release) Leukotriene C_4 (↓ release) Prostaglandin D_2 (↓ release) Tryptase (↓ release)	↓ Early-phase response severity
Mast cell and/or basophil	TNF-α-induced RANTES (↓ release) GM-CSF (↓ release) IL-3 (↓ release) IL-4 (↓ release/generation) IL-13 (↓ release) IL-6 (↓ release) IL-8 (↓ release)	↓ IFC chemotaxis, recruitment, activation, and adhesion
Epithelial cell	Histamine-induced ICAM-1 (↓ expression) TNF-α-induced RANTES (↓ release)	↓ IFC adhesion ↓ Eosinophil infiltration
Endothelial cell	IL-6 (↓ release) IL-8 (↓ release) Histamine-induced P-selectin (↓ expression)	↓ Leukocyte adhesion to endothelial cells and diapedesis
Monocyte (PBMC)	IL-1β (↓ release) IL-18 (↓ release) IL-5 (↓ release)	↓ IFC migration and activation
Th2 T lymphocyte (from allergic patients)	IL-4 (↓ release) IL-13 (↓ release) IL-5 (↓ release)	↓ IFC recruitment and activation
Lymphocyte (T cell, B cell and/or NK cell)	Co-stimulatory molecule Ox40 [CD134] (↓ expression)	↓ Allergen-stimulated lymphocyte proliferation
Eosinophil (from allergic patients)	PAF (↓ activity) TNF-α (↓ activity) Superoxide (↓ synthesis)	↓ Chemotaxis ↓ Adhesion ↓ Cytotoxicity
Neutrophil	CD11b (↓ expression)	↓ Chemotaxis/cytotoxicity

ICAM-1, intracellular adhesion molecule-1; IFC, inflammatory cell; IL, interleukin; PAF, platelet-activating factor; RANTES (regulated on activation, normal T cell expressed and secreted); TNF, tumour necrosis factor (6–8,10–21).

Table 2 Comparative potency to block responses of chinese hamster ovary (CHO) cells containing a cloned human H_1-receptor (6)

Antihistamine	Potency (K_b, nM)	Relative rank (1–9)
Desloratadine	0.2	1
Loratadine	16	7
Azelastine	0.3	2
Mizolastine	0.8	3–4
Astemizole	0.8	3–4
Terfenadine	3	5
Ebastine	7.9	6
Cetirizine	19	8
Fexofenadine	23	9

K_b, base ionization constant.

than loratadine, cetirizine, or fexofenadine *in vitro* (6).

Several animal models have further demonstrated the antihistaminic potency of desloratadine (7). Desloratadine was approximately four times more potent than loratadine in inhibiting histamine-induced paw oedema in the mouse (ED_{50} of 0.15 mg/kg and 0.60 mg/kg, respectively; $P < 0.05$). Guinea pigs were protected from the lethal effects of histamine with an ED_{50} of desloratadine (0.15 mg/kg) two-fold lower than that of loratadine (0.37 mg/kg). The increase in microvascular permeability in response to a histamine challenge to the upper airway of guinea pigs was inhibited with topical desloratadine in a dose one-tenth that of loratadine ($ED_{50} = 0.9$ μg *vs.* 8.7 μg, respectively).

Anti-inflammatory profile

In vitro studies have shown that, in addition to its antihistaminic properties, desloratadine has direct effects on inflammatory mediators in human cells. Desloratadine inhibited IgE-mediated release of histamine, tryptase, leukotriene C_4 (LTC_4), and prostaglandin D_2 (PGD_2) from mast cells, and histamine and LTC_4 release were inhibited from peripheral blood basophils (8). Desloratadine also inhibited the release of interleukin (IL)-3, tumour necrosis factor-α (TNF-α), and granulocyte macrophage colony-stimulating factor (GM-CSF) from human mast cells (9). In cells with high-affinity receptors for IgE (*Fc*εRI) desloratadine reduced release of the TNF-α-induced chemokine, RANTES (regulated on activation, normal T cell expressed and secreted) (10).

Preincubation of mast cells and basophils with desloratadine suppressed IL-6 release by up to 40% and IL-8 release by up to 50%, the magnitude of suppression being concentration-dependent (11). Desloratadine inhibited both IgE-mediated and non-IgE-mediated release of the cytokines IL-4 and IL-13 by human basophils. It is important to

note that desloratadine was six to seven times more potent an inhibitor of IL-4 and IL-13 than of histamine or LTC_4 (12). Pretreatment of human basophils with desloratadine inhibited IL-4 expression by up to 80% (12).

Desloratadine also targets the proinflammatory mediators from other human cells involved in IgE allergic reactions. Incubation with desloratadine at a concentration of 10 μM significantly inhibited the induction of intracellular adhesion molecule-1 (ICAM-1), an index of airway cell activation, in human nasal epithelial cells (13). Desloratadine inhibited the TNF-α-stimulated release of RANTES in epithelial cells, suggesting the potential to decrease the infiltration of airways by eosinophils (10,14). Desloratadine inhibited the endothelial cell release of IL-6 and IL-8 (11), and of P-selectin (15), the latter of which is involved in both the adhesion of leukocytes to the endothelial cell and in diapedesis.

The lipopolysaccharide-induced release of IL-1β and IL-18 from human peripheral blood mononuclear cells (PBMCs) was inhibited by approximately one-third by preincubation with desloratadine at concentrations of 10^{-7}–10^{-5} M for 2 h (14). Culture of PBMCs from patients with allergy to wasp venom in the presence of desloratadine (1–10 μg/ml) significantly decreased the secretion of IL-5 (16).

In allergen-activated/ human lymphocytes (T cells, B cells, and/or natural killer cells), desloratadine significantly reduced expression of the costimulatory molecule Ox40 (CD134) and decreased lymphocyte proliferation (17). *In vitro* studies show that the release of cytokines, chemokines, and adhesion molecules is diminished by desloratadine (18). Culture of leukocytes from allergic patients for 2 weeks with desloratadine (10^{-7} M) led to a reduction in the stimulated secretion from Th2 T lymphocytes of IL-4 (by 55% (allergic rhinitis) and 39% (allergic asthma), respectively), of IL-13 (by approximately 40% in each group), and of IL-5 (by 61% in each group) (19). In contrast, culture of leukocytes from healthy controls with no history of allergy in the presence of desloratadine decreased the stimulated secretion of IL-4 by only 19% and increased that of IL-13 and IL-5 (19). In a study of eosinophils from patients with allergic rhinitis or allergic asthma, desloratadine (10^{-7}–10^{-5} M/l) inhibited eosinophil chemotaxis induced by platelet-activating factor, eosinophil adhesion induced by TNF-α, and superoxide generation induced spontaneously and by phorbol myristate acetate (20). Preincubation of neutrophils with desloratadine (10^{3}–10^{0} mM) for 1 h resulted in a down-regulation of the constitutive and inductive expression of CD11b and a decrease in the chemotactic and cytotoxic response to chemoattractants, such as aqueous pollen extracts (21).

Anti-inflammatory effects in atopic patients

In preliminary results from placebo-controlled studies, desloratadine 20 mg once daily appeared to modulate allergic inflammation *in vivo* in subjects with SAR. Supernatants of PBMCs from subjects given desloratadine for 1 week showed increased expression of interferon-γ (INF-γ) (Th1 cytokine) and decreased expression of IL-4, IL-5, and IL-10 (Th2 cytokines), compared with those of subjects administered placebo (22). During allergy season, a decrease in circulating levels of eosinophil and basophil progenitors is seen as these leave the bloodstream and enter allergically activated tissues. At the peak of ragweed season, after 2 weeks of dosing, placebo recipients showed the expected fall in the number of circulating eosinophil and basophil progenitors, which was greater than the fall in desloratadine recipients ($P = 0.013$) (23). These cells, harvested and tested *in vitro*, also released less histamine per colony when the patient was pretreated with desloratadine. The results of these studies suggest that desloratadine both modifies the cytokine balance and alters cellular shuttling in people with SAR.

Clinical efficacy

The clinical efficacy of desloratadine therapy is documented by the study of patients with allergic rhinitis and of patients with chronic idiopathic urticaria. In controlled clinical studies, once-daily desloratadine therapy relieved the nasal and non-nasal symptoms of perennial allergic rhinitis (24) and SAR (25), including congestion (7). In patients with SAR and concomitant asthma, once-daily desloratadine therapy reduced the use of inhaled albuterol (7). Furthermore, once-daily desloratadine therapy in patients with chronic idiopathic urticaria reduced pruritus, number of hives, size of the largest hive, and interference with sleep and daily activities (26). The use of desloratadine therapy in the treatment of SAR, including published clinical data and recent postmarketing data, is reviewed below.

Controlled clinical studies of desloratadine therapy in SAR

Two multicentre, randomized, double-blind studies, one conducted in the spring allergy season ($n = 346$) and one conducted in the autumn allergy season ($n = 328$) in the USA, compared the efficacy of desloratadine 5 mg and placebo, once daily for 14 days, in patients aged 12 years or older with moderate-to-severe SAR (25). The total symptom score (TSS) was assessed in the morning and the evening, and reflected the patient's recollection of

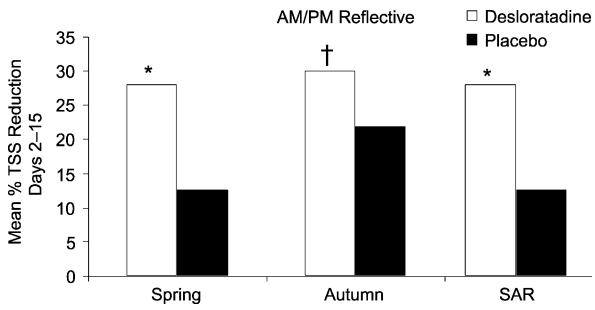

Figure 1 Desloratadine therapy in seasonal allergic rhinitis (SAR): mean percentage reduction in total reflective symptom scores (TSS) from baseline ($^{*}P < 0.01$; $\dagger P = 0.02$). Adapted from (25,30).

symptoms during the previous 12 h. The mean change from baseline in the reflective TSS averaged over the 2-week study period was the primary efficacy assessment. Desloratadine therapy produced a 28% (spring) and 30% (autumn) reduction in the TSS (Fig. 1) compared with 13% ($P < 0.01$ *vs.* desloratadine) and 22% ($P = 0.02$ *vs.* desloratadine) reduction with placebo. Most adverse events were mild to moderate in severity; headache, the most frequently reported adverse event, and somnolence, commonly associated with older antihistamines, occurred at similar rates with placebo and desloratadine treatment.

Relief of nasal congestion/stuffiness by once-daily desloratadine therapy was demonstrated in three multicentre, double-blind, placebo-controlled studies of patients with symptomatic SAR ($n = 300$ in each) (7). Twice daily, in the morning and the evening, nasal congestion/stuffiness was scored over a range of 0 (none) to 3 (severe), with the score refecting the patient's recollection of symptoms over the previous 12 h. Desloratadine therapy reduced mean baseline scores by 21.3–23.5%, which was significant compared with the 13.6–16.2% reduction in the placebo groups ($P < 0.05$).

Desloratadine therapy was compared with placebo in two multicentre, double-blind studies of patients with SAR and mild-to-moderate asthma, the results of which were pooled (27). Participants had at least a 2-year history of SAR and asthma, symptoms for at least 3 days before baseline assessment, and a forced expiratory volume in 1 s (FEV_1) of at least 70% of predicted value. Compared with placebo, desloratadine therapy was associated with a significant decrease from baseline in the mean asthma TSS beginning with the first dose and maintained over the 4 weeks of the study. The use of inhaled β_2-agonists was reduced significantly more with desloratadine therapy than with placebo.

Desloratadine, a nonsedating antihistamine, improves SAR symptoms without adversely affecting cognitive function. In a controlled comparison, patients with SAR who were symptomatic after priming with ragweed pollen were randomized to a single dose of desloratadine ($n = 81$), diphenhydramine ($n = 84$), or placebo ($n = 83$) (28). A battery of repeatable, automated, neuropsychological tests was administered at baseline and 90 min after dosing. There was no difference between desloratadine and placebo in any cognitive parameter, but the cognitive function of patients treated with diphenhydramine was significantly worsened, to a degree comparable to that caused by conditions such as mild head injury or migraine. Furthermore, on all parameters of vigilance, diphenhydramine produced clinically meaningful decrements, while desloratadine produced no significant change.

Postmarketing study of desloratadine therapy in SAR

At the launch of desloratadine in Germany in January 2001, an open-label, observational study was initiated to collect data on almost 50 000 patients with SAR (29). Data were recorded using a simple, modified, case report form. At the beginning and end of desloratadine therapy, patients used 4-point scales to separately rate the severity of nasal symptoms (nasal congestion, runny nose, sneezing/itching), ocular symptoms (watery eyes, burning/itching, redness), dermal symptoms (itching, hives/pustules, dryness), and asthma symptoms (wheeze, breathlessness, chest tightness, cough). Sum scores were calculated for each symptom category (nasal, ocular, dermal, asthma), and a TSS was calculated for the sum of individual category scores.

A total of 47 953 people participated in the study, 42% men and 58% women (mean age 38.8 years). Dermal symptoms were present in 39.3%. Use of asthma medication was reported by 7021 (15%) patients, but 19 512 (41.5%) reported at least one asthma symptom at baseline. The mean duration of desloratadine therapy was 38.4 days, and compliance was rated as good to excellent in 98% of patients.

Desloratadine 5 mg once daily significantly reduced sum scores for nasal symptoms, ocular symptoms, dermal symptoms, and asthma symptoms, and significantly reduced the TSS ($P = 0.0001$) (Table 3). The percentage of patients with moderate or severe nasal symptoms decreased more than tenfold, from 71.6% to 5.2% for rhinorrhoea, 73.7% to 5.2% for sneezing/itching, and 67.2% to 6.2% for nasal congestion following desloratadine. At the end of treatment, more than half (55.1%) of the patients had no nasal congestion compared with only 13.6% before treatment. Desloratadine therapy enabled half of the SAR patients with asthma symptoms at baseline to reduce their use of asthma medication.

Table 3 Decrease in SAR symptom scores with desloratadine therapy

Symptoms	Symptom score		
	Pretreatment	Post-treatment	Decrease (%)
Nasal	5.45	1.41	74.13*
Ocular	4.34	0.84	80.65*
Dermal	1.24	0.34	72.58*
Asthma†	3.68	1.01	72.55*
Total symptom score (TSS)	12.43	2.99	75.95*

*$P = 0.0001$.
†Subset of patients using asthma medication ($n = 7021$).
Reproduced from (29).

Patients and physicians rated the global efficacy, tolerability, and onset of action of desloratadine therapy compared with previously administered antihistamines including loratadine, cetirizine, fexofenadine, and others. Previous antihistamine therapy had been received by 17 513 (36.5%) patients, which was rated excellent or good for efficacy by 40.7% of patients. In contrast, more than 91% of patients (91.2%) and physicians (92.6%) judged desloratadine therapy excellent or good for efficacy. More than 98% of patients (98.5%) and physicians (98.9%) judged desloratadine excellent or good for tolerability, reflecting the low adverse event rate (0.44%). Onset of action of desloratadine was rated as faster than previous antihistamine therapy by 64.1% of doctors and 65.7% of patients.

Desloratadine improved quality of life by decreasing the impact of SAR symptoms on daily activities and sleep. During desloratadine therapy, SAR caused a moderate or severe interference with daily activities in only 3.0% of patients compared with 40.0% of patients before therapy and a moderate or severe disruption of sleep in only 2.6% of patients compared with 34.3% before therapy (Fig. 2).

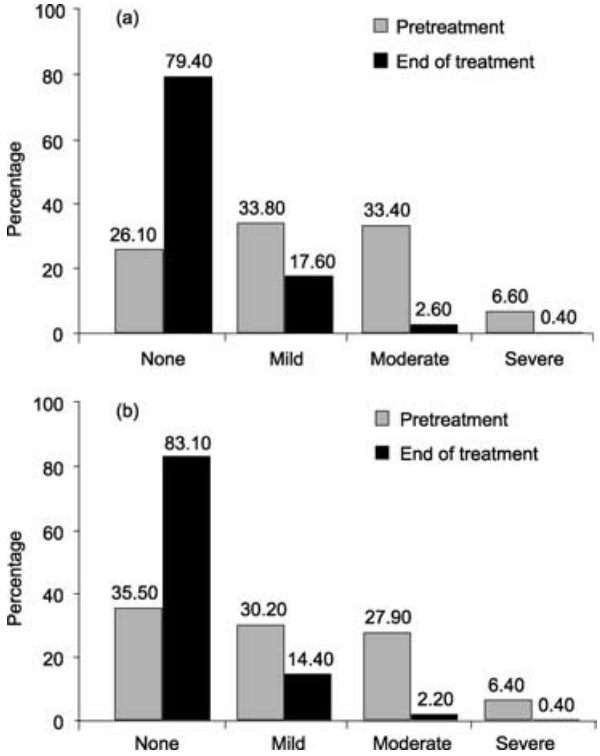

Figure 2 Desloratadine therapy in seasonal allergic rhinitis (SAR): SAR-related interference with (a) daily activities and (b) sleep disturbance before treatment and at the end of treatment. Adapted from (31).

Conclusions

Allergic rhinitis is a major chronic airway disease that negatively affects quality of life and represents a risk factor for asthma. Desloratadine, a potent, once-daily, orally active, nonsedating, histamine H_1-receptor antagonist inhibits multiple steps in the allergic inflammatory cascade *in vitro*. It is effective on nasal, ocular, dermal, asthma, and total symptoms, and is well tolerated. The inhibition of multiple steps in the allergy inflammatory cascade may provide an explanation for the broad clinical activity of desloratadine in the clinical setting. In SAR, desloratadine improves nasal, ocular, dermal, and asthma symptoms, decreases the use of asthma medication, and improves quality of life.

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