

Desloratadine activity in concurrent seasonal allergic rhinitis and asthma

Seasonal allergic rhinitis (SAR) and asthma, which are frequently comorbid, share some common allergic pathogenic bases. Clinical manifestations of these disorders might therefore be viewed as local manifestations of a systemic inflammatory state. Not only do the onsets of allergic rhinitis (AR) and asthma symptoms often coincide (within 1 year), but also nasal challenges with SAR allergens can induce airways hyperreactivity (AHR). Eosinophils, which are key effector cells in both SAR and asthma, cause AHR, tissue damage, and neuronal effects through secretion of toxic granule proteins, enzymes, and other mediators. The novel, nonsedating, histamine H₁-receptor antagonist, desloratadine, which exerts various favorable effects on the allergic cascade, significantly decreased SAR symptoms (e.g., nasal congestion) and diminished daily β_2 -agonist use and improved asthma symptoms, while maintaining pulmonary function, in patients with SAR-asthma who were treated with once-daily desloratadine regimens.

C. E. Baena-Cagnani

Division of Immunology and Respiratory Medicine,
Infantile Hospital, Córdoba, Argentina

Key words: allergic cascade; allergic rhinitis; asthma; desloratadine.

Carlos E. Baena-Cagnani, MD
Santa Rosa 381 (5000)
Córdoba
Argentina

Convergent lines of evidence from clinical, preclinical, and epidemiologic studies suggest that both seasonal allergic rhinitis (SAR) and asthma represent allergic conditions with shared components of airway hyperreactivity (AHR). In addition to the anatomic contiguity of upper and lower airways, and the physiologic links between them, nasal inflammation can also propagate AHR in the lower airways through systemic pathways (1). The symptoms of SAR and asthma can thus be viewed as distinct local manifestations of systemic inflammatory processes collectively termed the “allergic cascade”.

It has been estimated that approximately 60–80% of asthma patients experience symptoms of AR (2, 3). On the other hand, the proportion of AR sufferers with concomitant asthma (38%) far exceeds the overall prevalence of asthma in general populations (2). In a recent review (1), Togias termed AR virtually “ubiquitous” among patients with atopic asthma. Suboptimally managed AR can give rise to a number of comorbid inflammatory disorders, including otitis media and sinusitis, as well as asthma (4).

The International Study of Asthma and Allergies in Childhood (ISAAC) (5), which evaluated 463 801 children aged 13–14 years in 56 countries, has furnished robust evidence linking AR and asthma. For instance, multiple logistic regression analyses of responses to questionnaires completed by children in disparate geographic regions (e.g., Hong Kong and Kuwait) determined that a prior diagnosis of AR was associated with an odds ratio of 1.7 for a subsequent diagnosis of

asthma. Odds ratios for wheezing or severe wheezing episodes approached 3.0 in children with current rhinitis (6, 7).

Two particularly alarming trends that emerged from ISAAC were

- 1) an increase in asthma or wheezing as compared with prior epidemiologic data
- 2) a marked disparity between patient reports of asthma and the diagnosis rate for this condition.

A report of asthma underdiagnosis at the ISAAC center in São Paulo, Brazil (8), is of particular concern in light of the considerable asthma-specific mortality rates in Latin America, including a non-age-adjusted mortality rate of 5.63 per 100 000 in Uruguay and Mexico (9).

Additional support for the connection between AR and asthma derives in part from Scandinavian epidemiologic studies (3, 10, 11). First, Linna's group (10) reported that 14 (13%) of 110 Finnish children aged 3–17 years who had SAR at baseline developed asthma or wheezing within 11 years.

Second, of 82 Swedish patients available for follow-up more than a decade after being diagnosed with AR, 40% developed asthma or other lower-airway symptoms (11).

Third, Pedersen & Weeke (3) noted a strong temporal relationship in the onset of asthma and AR. Among 7662 Danish patients who presented with either AR or asthma (or both), 25% experienced onset of the two conditions within the same year, and, in 49% of patients

with concomitant AR and asthma, nasal symptoms preceded the onset of asthma. Three of every four patients who presented with AR or asthma experienced onset of the other condition within a 2-year interval. A prospective trial (12) involving 738 US college students followed for 23 years demonstrated that the incidence of new-onset asthma was nearly three times higher in young adults with AR at entry (10.5%) than in persons free of such symptoms (3.6%).

Further linking the pathogeneses of SAR and asthma are anatomic and physiologic considerations. Not only do the upper and lower airways share a common respiratory mucosa (13), but mouth breathing in the presence of nasal obstruction, as well as aspiration or postnasal drainage of nasal contents, can introduce allergens or inflammatory cells to the lower airway (2).

Nasal provocation with a seasonal allergen also significantly increased bronchial responsiveness to methacholine at both 30 min and 4.5 h in a randomized, double-blind, placebo-controlled trial (14). This rapid transition from introduction of nasal allergen to AHR is consistent with a nasal-bronchial reflex (2).

Moreover, in a methacholine-challenge study (15) involving 49 patients with SAR, 16 (33%) persons exhibited bronchial hyperresponsiveness (BHR) levels typical of individuals with asthma during the pollen season; that is, approximately twice the proportion of patients with BHR outside the SAR season. Conversely, a recent bronchial-biopsy study (16) demonstrated that segmental bronchial provocation induced nasal (and bronchial) symptoms, as well as eosinophil accumulation in both the bronchial and nasal mucosa, in nonasthmatic patients with AR.

Finally, histamine is also involved in the pathogenesis of asthma. Mast cells from asthmatic patients have shown increased activation and are more prone to release histamine than cells isolated from nonasthmatic persons: after endobronchial allergen challenge, increased levels of histamine were reported in the bronchoalveolar lavage fluid of patients with atopic asthma (17).

Removal of offending allergens, reduction of patients' exposure to these antigens, and treatment of SAR with antihistamines, topical corticosteroids, or immunotherapy can prevent or blunt BHR or overt asthma (18–21). The foregoing evidence, together with a solid body of immunohistopathologic and other experimental data, suggests that some symptoms of SAR-asthma can be ascribed to shared components of the allergic cascade, including effector cells and proinflammatory substances that mediate early and late-phase asthmatic responses.

Overview of the allergic cascade in SAR and asthma

The complexity of the allergic cascade opens many potential avenues for clinical interventions, which can conceivably be directed toward effector cells or

mediators (Fig. 1). In brief, allergens inhaled by the SAR-asthma patient diffuse across the epithelial airway mucosal lining and ligate IgE on the surfaces of submucosal mast cells. These effector cells rapidly degranulate, causing local, acute-phase symptoms through the release of histamine, bradykinin, and other proinflammatory mediators, including leukotrienes and prostaglandins.

The clinical manifestations of this event are twofold. First, during the early phase, these mediators induce bronchial smooth-muscle contraction; upregulate secretory activity of submucosal glands; cause neural involvement, with acute release of nerve growth factor (1); and increase bronchial-venule blood flow and permeability (22). Together with bronchial constriction, the foregoing effects lead to sneezing and sensory discomfort, edema, and elevated output of mucus, all of which can further compromise respiratory function by trapping air in the lungs (23).

Second, by a late-phase reaction associated with the release of cytokines and chemokines, such as eotaxin and RANTES (regulated on activation, normal T cell expressed and secreted), submucosal mast cells stimulate the proliferation, differentiation, and recruitment of eosinophils and helper T (T_H2) cells. Through the generation of cytokines, including interleukin-5 (IL-5), T_H2 cells assist in orchestrating these processes chronically (23).

A recent *in vivo* gene-transfer study conducted by Mould et al. (24) demonstrated that the presence of $CD4^+$ T cells, IL-5, and eotaxin was necessary in order for inhaled allergens to induce degranulation of eosinophils and AHR. Eosinophil chemotaxis caused by eotaxin was also amplified by IL-5.

The characteristic airways inflammation associated with asthma can be ascribed largely to chronic eosinophilia and residence of T_H2 cells. Either directly or indirectly, enzymes and toxic degranulation products released by eosinophils, such as major basic protein (MBP), eosinophil protein X, and eosinophil cationic protein, can injure local tissues and promote AHR. First, proteolytic enzymes mediate potentially irreversible lower-airways remodeling (25), and MBP directly induces AHR (26, 27).

The pivotal role of eosinophils, as well as mast cells, in causing BHR was underscored by a trial including 30 patients with SAR or asthma (28). In these individuals, methacholine PD_{20} values varied inversely with sputum eosinophil counts ($r = -0.52$, $P < 0.005$) and mast-cell counts ($r = -0.44$; $P < 0.02$). Second, because certain neuropeptides (e.g., vasoactive intestinal peptide) promote airway caliber, enzymatic degradation of these substances could also contribute to the pathogenesis of BHR (29). Finally, release by sensory neurons of substance P and other neuropeptides can exert additional inflammatory effects (23), a process termed neurogenic inflammation (1).

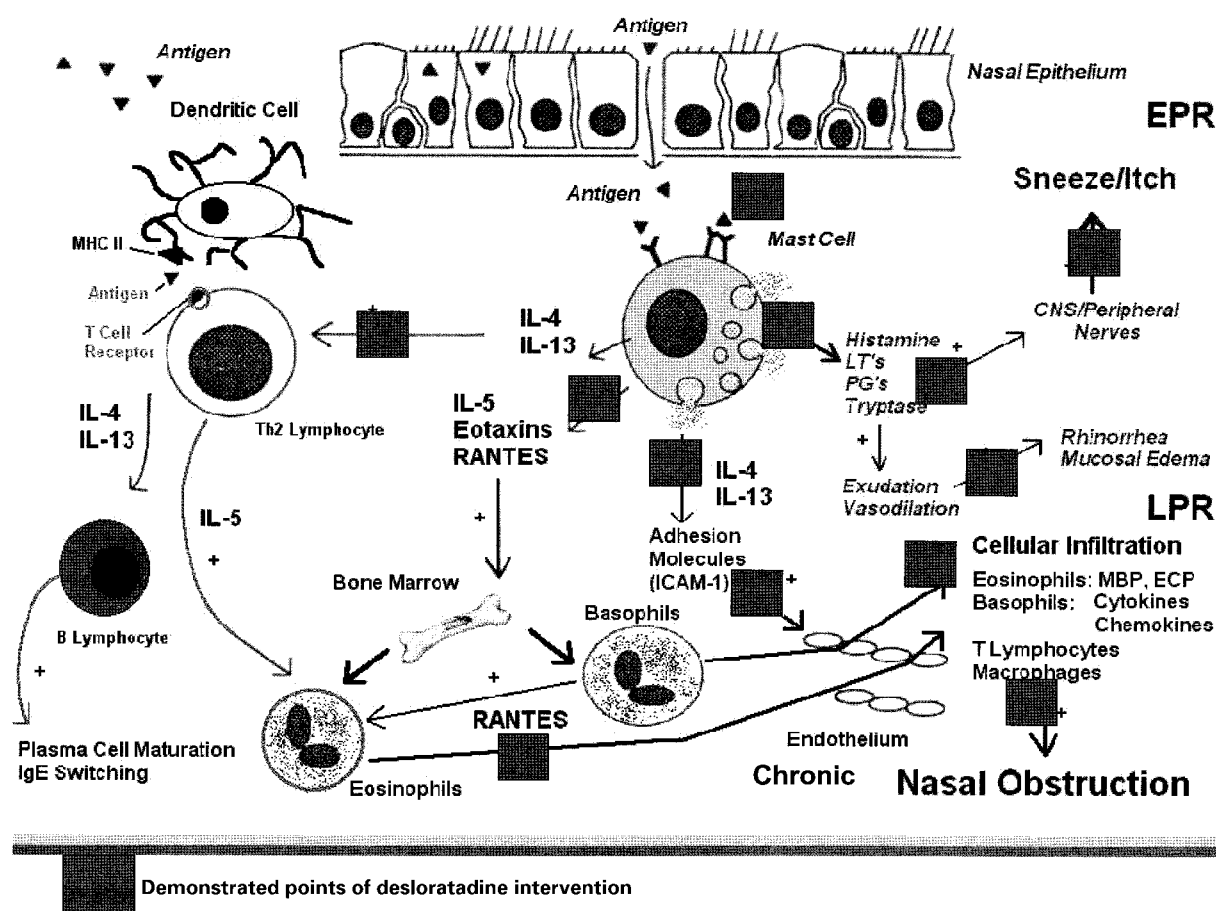


Figure 1. Intervention points in allergic cascade.

Effects of desloratadine on the allergic cascade

Evidence from both *in vitro* and *in vivo* studies demonstrated that desloratadine attenuates the pro-inflammatory functions of effector cells and their mediators while maintaining pulmonary function. Preclinical work in a primate model demonstrated that desloratadine significantly relieved bronchospasm, with favorable effects on airways compliance and resistance during provocation (30).

Desloratadine also attenuated important functions of eosinophils when these cells were incubated at pharmacologic concentrations (10 μ M) of this new potent molecule (31). First, chemotaxis induced by platelet-activating factor was significantly decreased (as compared with buffer) by a maximum of 36% ($\pm 8\%$). Second, desloratadine also significantly decreased TNF- α -induced adhesion of eosinophils to endothelial cells, the first step in the diapedesis of these effector cells. Third, significant suppressive effects of desloratadine on spontaneous and stimulated generation of toxic oxygen free radicals were also noted (31).

Finally, desloratadine, which binds to histamine H₁ receptors with among the highest affinities of antihistamines evaluated to date (32), also markedly diminished the release of numerous proinflammatory

mediators. In cell cultures, desloratadine significantly reduced release of the chemokine RANTES, cytokines (IL-6, IL-8), eicosanoids (such as PGD₂), and histamine, as well as the expression of ICAM-1 (33–36).

Effects of desloratadine on SAR-asthma: clinical studies

Desloratadine significantly relieves symptoms of both SAR and asthma in patients with both conditions, according to findings from a number of clinical trials. Entry criteria for each of these multicenter, randomized, double-blind, placebo-controlled studies included a minimum age of 15 years and a minimum 2-year history of SAR-asthma, with mild-to-moderate severity asthma symptoms that worsened during the autumn/winter allergy season.

Suitable for enrollment were patients with clinically symptomatic SAR (moderate rhinorrhea), asthma symptoms managed with p.r.n. β_2 -agonist reliever alone, a forced expiratory volume in 1 s (FEV₁) value of at least 70% of predicted, and a positive skin test for a seasonal allergen within 1 year before study onset. Patients using corticosteroids, antihistamines, or decongestants via any route, or more than 12 daily albuterol inhalations, were deemed ineligible, as were individuals with clinically significant comorbidity apart from SAR-asthma.

Each 4-week trial consisted of a 3- to 4-day run-in during which baseline symptoms were rated by patients on a 4-point scale (0: none, 3: severe). Instantaneous ratings were recorded at the end of the dosing interval, prior to the morning dose; these data enable effective assessment of efficacy at the end of the 24-h dosing interval, where some agents exhibit reduced therapeutic coverage. The two 12-h ratings were averaged to provide a single AM/PM reflective score. Studies were conducted during the autumn/winter allergy season.

Asthma symptoms comprised cough, wheeze, and difficulty in breathing, the sum of which formed the total asthma symptom score (TASS). Symptoms of SAR were divided into “nasal”, which included rhinorrhea, itching, congestion/stuffiness, and sneezing; and “non-nasal”, which comprised ocular itching/burning, tearing/watery eyes, redness of eyes, and pruritus of the ears and/or palate. The principal outcome variable was the change from baseline in TASS or total (SAR) symptom score (TSS) after 2–4 weeks of desloratadine (5 mg q.d.) therapy or placebo. Active-treatment and control groups were well balanced with regard to demographic and other baseline characteristics in each clinical trial.

SAR symptoms

Once-daily therapy with desloratadine significantly relieved SAR in a study involving 311 patients SAR-asthma patients. As compared with differences from baseline in the placebo group at weeks 1–2 and 1–4, desloratadine patients exhibited greater improvements in total nasal ($P < 0.013$) and nonnasal ($P < 0.001$) symptom scores (Fig. 2) (37).

The reflective TSS declined from baseline by approximately 31–35% at weeks 1–2 and 1–4, respectively, in the desloratadine group, and 20–25% in the

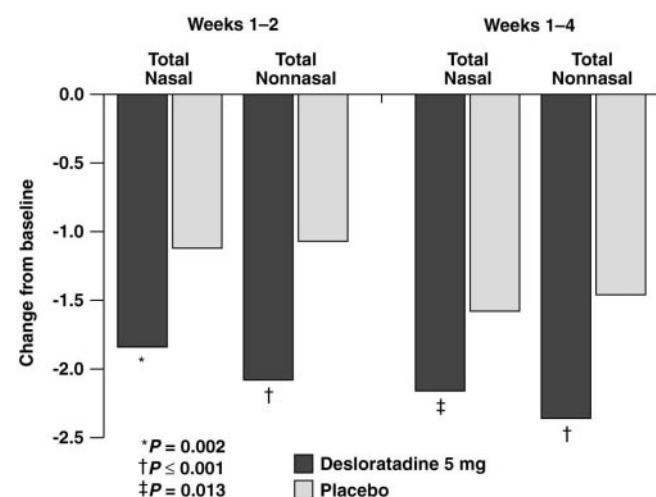


Figure 2. Change from baseline in average AM instantaneous total nasal and nonnasal symptom scores. With permission of Schenkel et al. (37).

Table 1. Changes from baseline in patient-evaluated average AM/PM reflective total seasonal allergic rhinitis symptom scores

Time point	Desloratadine, 5 mg q.d.			Placebo			P value
	n	Change	% Change	n	Change	% Change	
Baseline	166	15.45	—	160	15.43	—	—
Day 1	161	−3.13	−20.6	156	−1.06	−7.2	<0.001
Day 2	164	−3.72	−24.7	160	−1.51	−10.8	<0.001
Day 3	164	−4.12	−27.1	159	−1.93	−13.1	<0.001
Day 4	164	−4.59	−30.0	158	−2.13	−14.2	<0.001

With permission of Schenkel et al. (37).

control arm at the same time points ($P < 0.001$ for each intergroup comparison). As early as desloratadine treatment day 1 – within 12 h after the first dose – active therapy decreased the TSS from baseline by 20.6%, as compared with a 7.2% fall in the control group ($P < 0.001$) (Table 1) (37).

Similar findings were reported by Nathan et al. (38), who evaluated the effect of desloratadine on nasal congestion in 613 patients with a minimum 2-year history of SAR or asthma, as well as a 3-day history of both conditions. As with the TSS, decreases from baseline in reflective nasal congestion scores were significantly more marked in the desloratadine group than controls after 1–2 to 1–4 weeks. The onset of a significant decongestant effect was observed as early as desloratadine treatment day 1.

Asthma symptoms

A pooled analysis (39) of two multicenter trials involving 613 patients with SAR and asthma of mild-to-moderate severity demonstrated that desloratadine effectively relieved asthma symptoms. Consistent with its effects on SAR symptoms, including nasal congestion, desloratadine (5 mg q.d.) produced significantly sharper decreases from baseline in reflective TASS values than placebo at weeks 1–2 ($P = 0.003$) and 1–4 ($P = 0.022$) (39). A significant antiasthmatic effect for desloratadine was observed as early as treatment day 1, within 12 h of the first dose (Fig. 3) (39).

As compared with placebo, the once-daily desloratadine regimen significantly reduced β_2 -agonist use for control of asthma symptoms, while maintaining FEV₁ (Fig. 4). Decreases from baseline for mean number of β_2 -agonist inhalations in the desloratadine and placebo groups were approximately 14% and 7%, respectively, over weeks 1–2 ($P < 0.001$); corresponding decreases over weeks 1–4 were about 12% and 10% ($P = 0.003$) (39).

Similar effects were recorded in a recent 4-week study (40) of 208 men and 396 women with a minimum 2-year history of SAR and mild-to-moderate asthma. As compared with changes from baseline in the control group, mean AM/PM reflective TASS and daily β_2 -agonist inhalations decreased significantly over weeks 1–2 and 1–4. No significant intergroup differences in FEV₁ were observed.

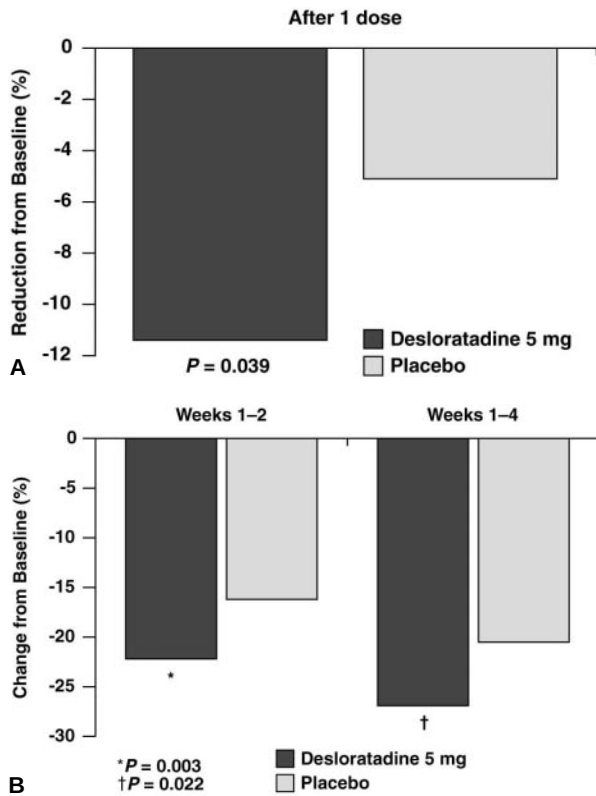


Figure 3. Percent reduction in instantaneous AM (A) and AM/PM reflective (B) total asthma scores. With permission of Ratner et al. (39).

In the foregoing clinical trials, desloratadine was safe and well tolerated. Incidences of adverse events were similar in both the active-treatment and placebo arms. Headache was the only treatment-emergent adverse event experienced by more than 5% of patients, but the incidences were similar in the active-treatment and placebo groups (37). No clinically significant changes in electrocardiography (e.g., QT_c interval) or laboratory parameters were observed.

The decongestant effects, rapid onset of decongestant activity within 1 day, and capacity to diminish β_2 -agonist use for asthma symptom control significantly in patients with SAR-asthma are unprecedented among the earlier, second-generation histamine H₁-receptor antagonists. By reducing nasal congestion, desloratadine therapy also diminishes the likelihood of mouth breathing and, with it, the prospect of sustained allergen introduction to the lower airway.

Treatment of SAR-asthma patients with cetirizine at 10 mg q.d. ($n=93$) significantly reduced TSS from baseline at weeks 1–4 (of 6 total weeks) as compared with placebo ($n=93$). However, there were no significant between-group differences in nasal congestion scores at any time point (41).

In a smaller, 26-week study (42) involving 28 patients with AR-asthma, cetirizine therapy (20 mg q.d.)

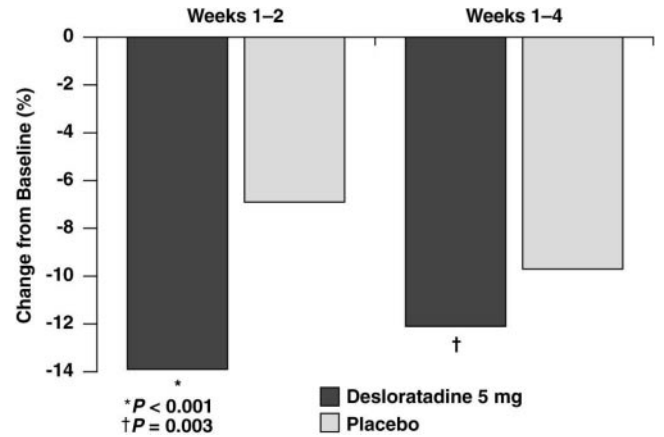


Figure 4. Percent reduction in mean number of puffs of inhaled β_2 -agonists. With permission of Ratner et al. (39).

effectively, but inconsistently, relieved a number of AR and asthma symptoms: significant treatment effects were observed at only selected assessments. For instance, a significant decongestant effect was not observed with cetirizine treatment until the seventh of 13 biweekly assessments and at two other time points.

Neither of these trials (41, 42) showed significant intergroup differences in albuterol use (or spirometric lung-function parameters) with cetirizine as compared with placebo. Apart from desloratadine, antihistamines that enhance pulmonary function do so at supratherapeutic doses or with unacceptable untoward effects (43).

Conclusions

According to compelling evidence from clinical, pre-clinical, and epidemiologic studies, SAR and asthma have certain shared allergic foundations, and symptoms of these conditions may represent distinct local manifestations of a systemic inflammatory state. Not only are SAR and asthma frequently comorbid, exhibiting temporal associations in initial symptom onset, but nasal provocation with SAR allergens can cause BHR. Airways eosinophilia, in concert with residence of T_H2 cells, may be instrumental in propagating chronic asthma symptoms in susceptible individuals. Eosinophils, which are key effector cells in both SAR and asthma, cause AHR, tissue damage, as well as neuronal effects that can further amplify the inflammatory response, through secretion of toxic granule proteins, enzymes, and other mediators. The novel, nonsedating histamine H₁-receptor antagonist, desloratadine, markedly blunted both eosinophil functions and proinflammatory mediator release *in vitro*. Once-daily desloratadine therapy significantly decreased SAR symptoms (e.g., nasal congestion) and diminished daily β_2 -agonist use and improved asthma symptoms in patients with SAR-asthma.

References

1. TOGIAS A. Unique mechanistic features of allergic rhinitis. *J Allergy Clin Immunol* 2000;**105**(6 Pt 2):S599–S604.
2. CORREN J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997;**99**:S781–S786.
3. PEDERSEN PA, WEEKE ER. Asthma and allergic rhinitis in the same patients. *Allergy* 1983;**38**:25–29.
4. SETTIPANE RA. Complications of allergic rhinitis. *Allergy Asthma Proc* 1999;**20**:209–213.
5. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;**351**(9111):1225–1232.
6. BEHBEHANI NA, ABAL A, SYABBALO NC, ABD AA, SHAREEF E, AL MOMEN J. Prevalence of asthma, allergic rhinitis, and eczema in 13- to 14-year-old children in Kuwait: an ISAAC study. *International Study of Asthma and Allergies in Childhood. Ann Allergy Asthma Immunol* 2000;**85**:58–63.
7. LEUNG R, WONG G, LAU J, et al. Prevalence of asthma and allergy in Hong Kong schoolchildren: an ISAAC study. *Eur Respir J* 1997;**10**:354–360.
8. SOLÉ D, YAMADA E, VANA AT, COSTA-CARVALHO BT, NASPITZ CK. Prevalence of asthma and related symptoms in school-age children in São Paulo, Brazil – International Study of Asthma and Allergies in Children (ISAAC). *J Asthma* 1999;**36**:205–212.
9. NEFFEN H, BAENA-CAGNANI CE, MALKAL S, et al. Asthma mortality in Latin America. *J Investig Allergol Clin Immunol* 1997;**7**:249–253.
10. LINNA O, KOKKONEN J, LUKIN M. A 10-year prognosis for childhood allergic rhinitis. *Acta Paediatr* 1992;**81**:100–102.
11. DANIELSSON J, JESSEN M. The natural course of allergic rhinitis during 12 years of follow-up. *Allergy* 1997;**52**:331–334.
12. SETTIPANE RJ, HAGY GW, SETTIPANE GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;**15**:21–25.
13. ROWE-JONES JM. The link between the nose and lung, perennial rhinitis and asthma – is it the same disease? *Allergy* 1997;**52** Suppl 36:20–28.
14. CORREN J, ADINOFF AD, IRVIN CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992;**89**:611–618.
15. DI LORENZO G, MANSUETO P, MELLUSO M, et al. Non-specific airway hyperresponsiveness in mono-sensitive Sicilian patients with allergic rhinitis. Its relationship to total serum IgE levels and blood eosinophils during and out of the pollen season. *Clin Exp Allergy* 1997;**27**:1052–1059.
16. BRAUNSTAHL GJ, KLEINJAN A, OVERBEEK SE, PRINS JB, HOOGSTEDEN HC, FOKKENS WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;**161**:2051–2057.
17. WENZEL SE, LARSEN GL, JOHNSTON K, VOELKEL NF, WESTCOTT JY. Elevated levels of leukotriene C₄ in bronchoalveolar lavage fluid from atopic asthmatics after endobronchial allergen challenge. *Am Rev Respir Dis* 1990;**142**:112–119.
18. CORREN J, HARRIS AG, AARONSON D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997;**100**(6 Pt 1):781–788.
19. CORREN J, ADINOFF AD, BUCHMEIER AD, IRVIN CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;**90**:250–256.
20. PAUWELS R. Influence of treatment on the nose and/or the lungs. *Clin Exp Allergy* 1998;**28** Suppl 2:37–40.
21. OLIVIERI M, MOHADDES ZADEH MR, TALAMINI G, LAMPONTI G, LO CV. Local nasal immunotherapy and bronchial hyperreactivity in seasonal allergic rhinitis: an observational pilot study. *J Investig Allergol Clin Immunol* 2000;**10**:300–304.
22. BARNES PJ. Inflammatory mediator receptors and asthma. *Am Rev Respir Dis* 1987;**135**(6 Pt 2):S26–S31.
23. Allergy and hypersensitivity. In: JANEWAY CA Jr, TRAVERS P, WALPORT M, CAPRA JD, editors. *Immunobiology: the immune system in health and disease*. New York: Elsevier Science/Garland Publishing, 1999:461–488.
24. MOULD AW, RAMSAY AJ, MATTHAEI KI, YOUNG IG, ROTHENBERG ME, FOSTER PS. The effect of IL-5 and eotaxin expression in the lung on eosinophil trafficking and degranulation and the induction of bronchial hyperreactivity. *J Immunol* 2000;**164**:2142–2150.
25. HOLGATE ST, LACKIE PM, DAVIES DE, ROCHE WR, WALLS AF. The bronchial epithelium as a key regulator of airway inflammation and remodelling in asthma. *Clin Exp Allergy* 1999;**29** Suppl 2:90–95.
26. GUNDEL RH, LETTS LG, GLEICH GJ. Human eosinophil major basic protein induces airway constriction and airway hyperresponsiveness in primates. *J Clin Invest* 1991;**87**:1470–1473.
27. FLAVAHAN NA, SLIFMAN NR, GLEICH GJ, VANHOUTTE PM. Human eosinophil major basic protein causes hyperreactivity of respiratory smooth muscle. Role of the epithelium. *Am Rev Respir Dis* 1988;**138**:685–688.
28. FORESI A, LEONE C, PELUCCI A, et al. Eosinophils, mast cells, and basophils in induced sputum from patients with seasonal allergic rhinitis and perennial asthma: relationship to methacholine responsiveness. *J Allergy Clin Immunol* 1997;**100**:58–64.
29. BARNES PJ. Neuropeptides and asthma. *Am Rev Respir Dis* 1991;**143**(3 Pt 2):S28–S32.
30. KREUTNER W, HEY JA, ANTHES J, BARNETT A, YOUNG S, TOZZI S. Preclinical pharmacology of desloratadine, a selective and non-sedating histamine H₁ receptor antagonist. 1st communication: receptor selectivity, antihistaminic activity, and antiallergenic effects. *Arzneimittelforschung/drug Res* 2000;**50**:345–352.
31. AGRAWAL DK, BERRO A, TOWNLEY RG. Desloratadine attenuation of eosinophil chemotaxis, adhesion, and superoxide generation. Presented at XIXth Congress of European Academy of Allergology and Clinical Immunology, 1–5 July 2000, Lisbon, Portugal.
32. ANTHES J, RICHARD C, WEST RE, et al. Functional characterization of desloratadine and other antihistamines in human histamine H₁ receptors. Presented at XIXth Congress of the European Academy of Allergology and Clinical Immunology, 1–5 July 2000, Lisbon, Portugal.
33. LEBEL B, BOUSQUET J, CZARLEWSKI W, et al. Loratadine (L) reduces RANTES release by an epithelial cell line. *J Allergy Clin Immunol* 1997;**99**(Pt 2):S44 (Abstract 1802).
34. GENOVESE A, PATELLA V, DE CRESCENZO G, DE PAULIS A, SPADARO G, MARONE G. Loratadine and desethoxycarbonyl-loratadine inhibit the immunological release of mediators from human Fc epsilon RI+ cells. *Clin Exp Allergy* 1997;**27**:559–567.
35. LIPPERT U, KRUGER-KRASAGAKES S, MOLLER A, KIESSLING U, CZARNETZKI BM. Pharmacological modulation of IL-6 and IL-8 secretion by the H₁-antagonist decarboethoxy-loratadine and dexamethasone by human mast and basophilic cell lines. *Exp Dermatol* 1995;**4**(4 Pt 2):272–276.

36. VIGNOLA AM, CRAMPETTE L, MONDAIN M, et al. Inhibitory activity of loratadine and descarboethoxyloratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. *Allergy* 1995;**50**:200–203.
37. SCHENKEL E and the Desloratadine Study Group. Desloratadine improved SAR symptoms in patients with mild-to-moderate asthma and SAR. Presented at annual meeting of American College of Allergy, Asthma and Immunology, 5–8 November 2000, Seattle, WA.
38. NATHAN R and the Desloratadine Study Group. Desloratadine relieved nasal congestion in patients with seasonal allergic rhinitis and concurrent asthma. Presented at annual meeting of American College of Allergy, Asthma, and Immunology, 5–8 November 2000, Seattle, WA.
39. RATNER PH and the Desloratadine Study Group. Desloratadine improved asthma symptoms and reduced bronchodilator use in 2 studies of patients with asthma and SAR. Presented at annual meeting of American College of Allergy, Asthma and Immunology, 5–8 November 2000, Seattle, WA.
40. BAENA-CAGNANI C and the Desloratadine Study Group. Desloratadine improved asthma symptoms and decreased beta₂-agonist use in patients with seasonal allergic rhinitis and concomitant asthma. Submitted to the XXth Congress of European Academy of Allergology and Clinical Immunology, 9–13 May 2001, Berlin, Germany.
41. GRANT JA, NICODEMUS CF, FINDLAY SR, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995;**95**(5 Pt 1):923–932.
42. AARONSON DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol* 1996;**76**:440–446.
43. BECKMAN DB, GRAMMER LC. Pharmacotherapy to prevent the complications of allergic rhinitis. *Allergy Asthma Proc* 1999;**20**:215–223.