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Decongestant efficacy of desloratadine in patients with seasonal allergic rhinitis

Recent advances in experimental immunologic approaches to seasonal allergic rhinitis (SAR) have led to a shift in the concepts of its pathogenesis. The conventional view of SAR as a local response to inhaled allergens has largely given way to a new view of this disorder as a systemic condition with local tissue manifestations. This concept, together with an increasing recognition of specific mediators' distinct roles in driving the early- and late-phase allergic responses, has opened multiple lines of therapeutic attack within the allergic cascade. Potent inhibition of inflammatory mediator release at distinct points in this cascade is conferred by desloratadine. In addition to the familiar range of SAR symptoms amenable to antihistamine therapy, desloratadine uniquely attenuates patient ratings of nasal congestion. This novel, nonsedating histamine H_1-receptor antagonist is the only once-daily antiallergic product with a consistent decongestant effect that begins within hours of the first morning dose and is sustained for the entire treatment period.

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Progress in the immunohistology of seasonal allergic rhinitis (SAR), together with the development of refined nasal-challenge models, has substantially clarified the pathogenesis of this disorder, particularly within the past 15 years (1–4). Elucidation of the complex effector mechanisms underlying SAR and other inflammatory conditions has occasioned a fundamental departure in both experimental and clinical approaches to SAR. Once viewed as a predominantly local reaction to inhaled allergens, SAR is increasingly being seen as a systemic condition with diverse, often comorbid, local effects on the airways.

This emerging approach to SAR as a systemic condition has also introduced the concept of mediator specificity: the distinct roles of cytokines, chemokines, adhesion molecules, and other mediators in regulating complex interactions among effector cells. These include mast cells, basophils, eosinophils, T cells, and other leukocytes, as well as epithelial and endothelial cells. The proinflammatory mediators include histamine; lipid mediators, such as leukotrienes (e.g., LTC_4) and prostaglandins (e.g., PGE_2); cytokines, such as interleukins and tumor necrosis factor-alpha (TNF-α); chemokines, such as eotaxins and RANTES (regulated on activation, normal T-cell expressed and secreted); and adhesion molecules, such as the selectins and intercellular adhesion molecule-1 (ICAM-1).

This conceptual shift enables targeting of multiple points of therapeutic attack within the allergic cascade. For instance, interleukin-1β (IL-1β) and TNF-α have been isolated in nasal secretions from patients with allergic rhinitis (AR) (5). Each of these cytokines upregulates allergen-induced expression of the adhesion molecule E-selectin by endothelial cells, enabling leukocytes to interact with these cells and migrate across the airway vascular endothelium. Work involving nasal mucosal cells from patients with AR has demonstrated that exposure of these cells to soluble IL-1 receptors and TNF-binding proteins (5) markedly suppresses E-selectin induction *in vitro*. These approaches, along with others, such as anti-IL-5 monoclonal antibodies, sIL-4 receptors, and anti-VLA-4 (very late activation antigen-4), thus represent plausible lines of potential pharmacologic attack.

Interestingly, recent experimental and clinical work indicates that desloratadine potently inhibits the allergic cascade at many points and significantly relieves symptoms of SAR, including nasal congestion.

Overview of the pathophysiology of nasal congestion

Key effector mechanisms in the allergic cascade

The complex immunopathogenesis of type I allergic inflammation in the nose is illustrated in Fig. 1 (courtesy of Dr Ruby Pawankar) (6). Acute symptoms typically experienced by SAR sufferers within the first 30 min (e.g., wheeze, cough, rhinorrhea, and congestion) result when the host initiates the acute-phase allergic response after inhalation of pollen allergens (e.g., ragweed) (7). However, after diffusing across the nasal mucosa, these allergens – through the actions of

cytokines – also induce naive, antigen-specific CD4 T cells to develop into helper T (T_H2) cells (7).

T_H2 cells, in turn, trigger an isotypic class switch, such that antigen-specific B cells (plasma cells) generate IgE antibodies, which bind to IgE receptors on mast cells resident in airway mucosal tissues (7). Cross-linkage by allergens of IgE bound to high-affinity FcεRI receptors on the surfaces of mast cells (as well as basophils and eosinophils) causes these cells to secrete proinflammatory mediators, which amplify the ongoing IgE response and promote both proliferation and recruitment of eosinophils and other effector cells. Acting in concert, these substances increase local blood flow and vascular permeability, stimulate excessive secretion of mucus, and reduce airway patency, leading to sneezing, rhinorrhea, obstruction, and chronic nasal congestion.

Nasal congestion illustrates the complexity and many levels of amplification that are hallmarks of the inflammatory response in SAR. For instance, patients with AR (and nonallergic controls) experienced nasal congestion, as well as rhinorrhea and sore throat, when challenged with PGD_2, histamine, or bradykinin; each of these substances decreased nasal patency (8).

In addition to these three proinflammatory mediators, yet another – IL-4 – caused a dose-limiting subjective sensation of nasal congestion within 24 h and increased nasal-lavage histamine content when administered systemically (at $\geq$3 μg/kg t.i.d.) to patients being treated for carcinoma (9). Therapy with IL-4 for 3 days after a histamine challenge caused vascular unresponsiveness to histamine.

Activation of T_H2 cells and degranulation by mast cells during the early-phase response paves the way for infiltration of airway tissue by key effector cells, including eosinophils, T_H2 cells, and basophils. Extravasation and persistent tissue residence of these effector cells occur during the late-phase inflammatory response (4–12+ h after inhalation of allergen) and may be associated with chronic symptoms such as nasal obstruction and difficulty in breathing (7).

Also instrumental to the migration of eosinophils and other effector cells to local sites of allergy is adhesion of these leukocytes to endothelial cells lining vessel walls. Leukocyte diapedesis occurs through interactions with surface molecules expressed by endothelial cells, including selectins (E-selectin, P-selectin) and intercellular adhesion molecule-1 (ICAM-1).

Effects of desloratadine on the allergic cascade

Desloratadine potently inhibits the allergic cascade at several loci, including both early- and late-phase responses.

First, desloratadine exhibited potent inhibition of ^{3}H-labeled pyrilamine H_1-receptor binding, with a K_i value of 0.87, in Chinese hamster ovary cells stably transfected with human H_1 receptors (CHO-H_1 cells)

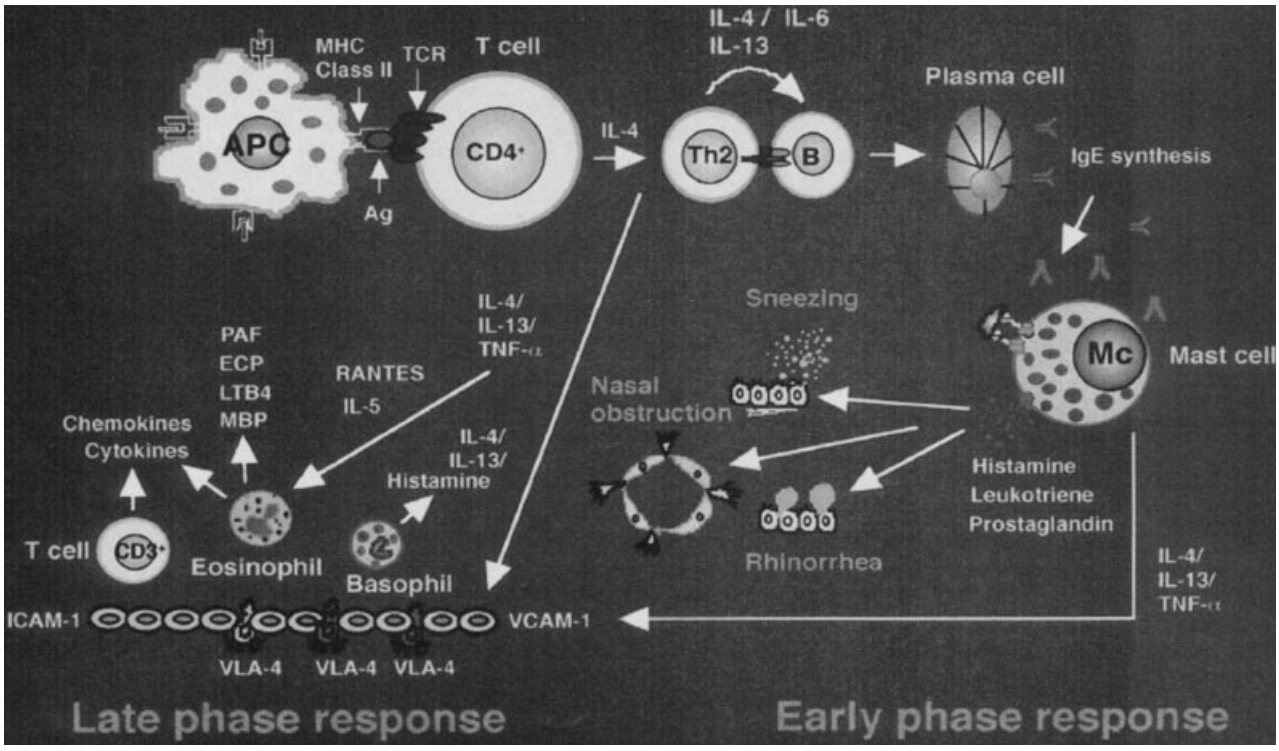

Figure 1. Mechanism of type I allergic reaction in the nose. Reproduced with permission from R. Pawankar (6), Blackwell Science Ltd, Oxford, UK.

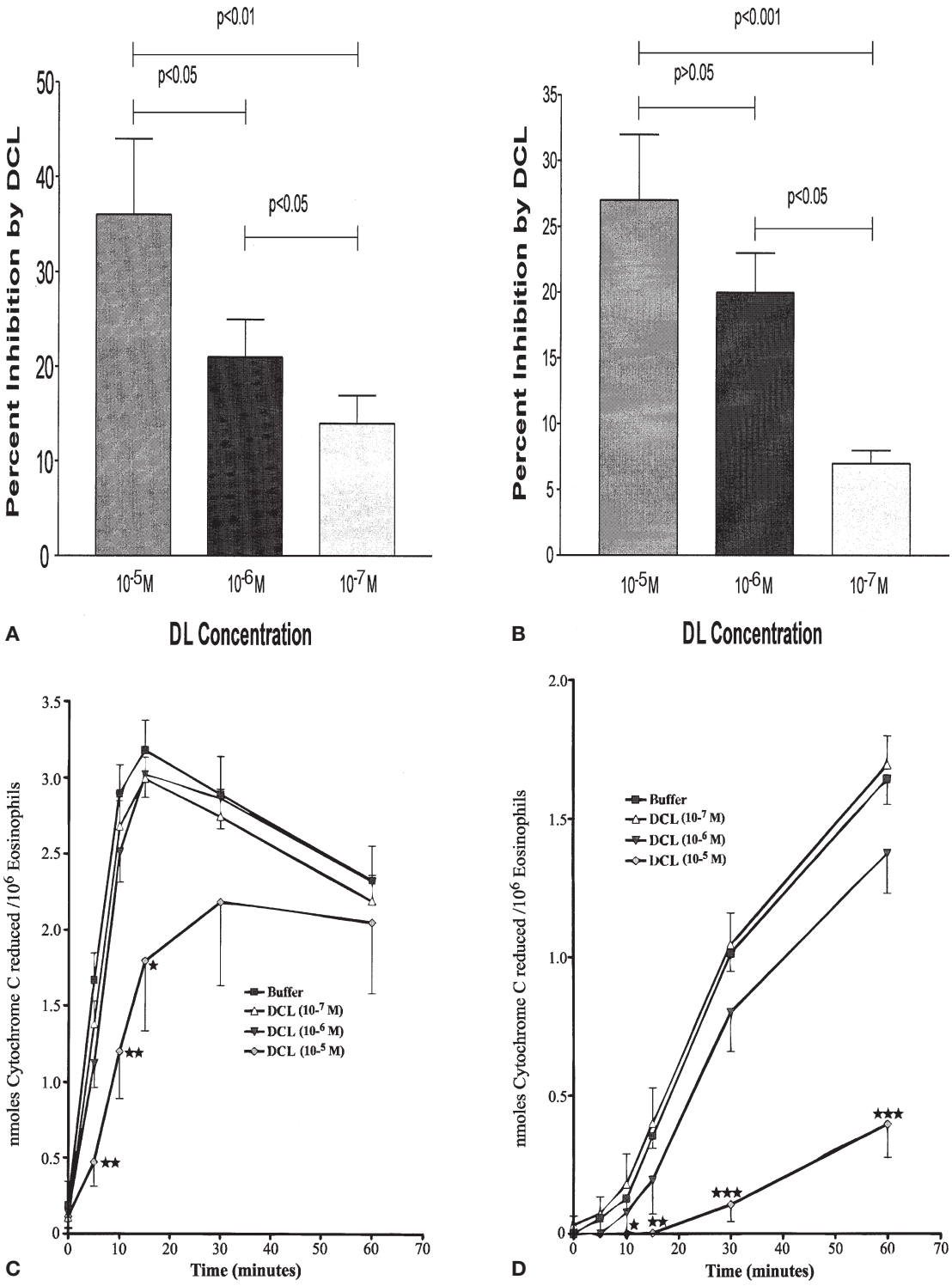

Figure 2. Effects of desloratadine on A) platelet-activating factor-induced eosinophil chemotaxis, B) ^{51}Cr-labeled eosinophil adhesion to human umbilical-vein endothelial cells, C) phorbol myristate acetate (PMA)-stimulated superoxide generation, and D) spontaneous superoxide generation. With permission of Agrawal et al. (20).

(10). On the basis of these data, we can say that desloratadine binds with high affinity to these receptors; that is, approximately 50–200 times more avidly than cetirizine or fexofenadine (Table 1).

Inhibition of histamine release by desloratadine was demonstrated in both human and rodent cell cultures. At micromolar drug concentrations, desloratadine rapidly induced significant (as compared with control

Table 1. Affinity constants obtained from ^{3}H-labeled pyrilamine binding to human recombinant histamine H_1 receptor from membranes of Chinese hamster ovary cells

Compound	K_i (nM ± SEM	Relative potency
Desloratadine	0.87 ± 0.1	201
Cetirizine	47.2 ± 10	3.7
Ebastine	51.7 ± 6.8	3.4
Fexofenadine	175 ± 68	1.0
Loratadine	138 ± 23	1.2
Mizolastine	22 ± 6	8.0
Pyrilamine	1.7 ± 0.1	103
Terfenadine	40 ± 4.6	4.4

SEM: standard error of mean.
With permission of Anthes et al. (10).

buffer) inhibition of both IgE-dependent and independent release of histamine from mixed peripheral-leukocyte preparations (11). Similar trends were observed when either anti-IgE-activated human basophils or 2,4-dinitrophenyl (DNP)-triggered rat basophilic leukemia (RBL-2H3) cells were incubated with desloratadine or loratadine at concentrations exceeding 2 and 7 μM, respectively (12).

The mechanism underlying these effects might involve desloratadine's capacity to mobilize cytosolic Ca^{2+} stores and attenuate the Ca^{2+} influx necessary for IgE-mediated degranulation and, with it, release of histamine and other proinflammatory mediators from effector cells (e.g., mast cells and basophils) (13). In a CHO line, desloratadine was a more potent antagonist of Ca^{2+} flux than cetirizine, fexofenadine, terfenadine, astemizole, or loratadine (14).

Second, Genovese et al. (15) observed that preincubation of cell cultures with desloratadine at pharmacologic concentrations of approximately 10 μM significantly inhibited the anti-FcεR1-induced release of histamine and LTC_4, as well as eicosanoid PGD_2 and tryptase, from basophils and mast cells derived from human skin and lung tissues.

Third, *in vitro* studies also showed that desloratadine markedly diminished the release of numerous cytokines, chemokines, and adhesion molecules that promote the proliferation and differentiation, as well as the tissue infiltration and recruitment, of key effector cells. For instance, incubation of epithelial cells (from nasal turbinates or polyps) with desloratadine at a concentration of 10 μM reduced histamine-induced membrane expression of ICAM-1 and human leukocyte class II (HLA-DR) antigen, two indices of airway epithelial-cell activation (16).

Desloratadine's potent anti-inflammatory effects in human mast cells, as well as basophils and endothelial cells, were demonstrated by the agent's inhibitory effects on histamine- or phorbol myristate acetate (PMA)-stimulated IL-6 and IL-8 release (17), which reached 50% at a concentration of approximately two to five orders of magnitude lower than that of

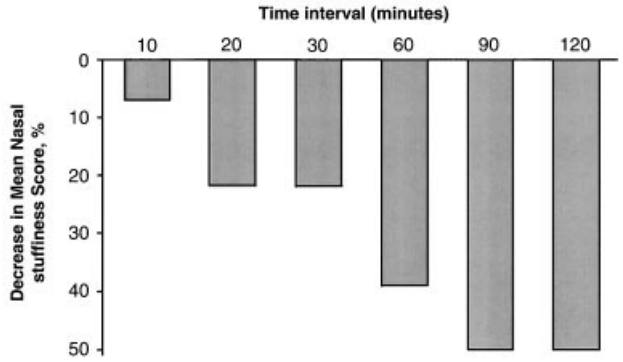

Figure 3. Percent change in nasal stuffiness scores (maximum: 3) after allergen challenge and desloratadine dosing on day 1 among 2-point responder group ($n = 14$). With permission of Horak et al. (25).

loratadine in a human umbilical-vein endothelial cell (HUVEC) preparation (18). At nanomolar concentrations, desloratadine also significantly inhibited expression by HUVECs of P-selectin (18), which promotes leukocyte adhesion to endothelial cells and diapedesis.

Inhibition by desloratadine of TNF-α-stimulated release of RANTES by epithelial cells *in vitro* (19) suggests that desloratadine can potentially diminish airways infiltration by eosinophils. Three inflammatory functions were attenuated by desloratadine when introduced to eosinophils isolated from 10 patients with AR or AR plus asthma (20).

First, chemotaxis of human eosinophils in response to the lipid mediator platelet-activating factor was significantly suppressed by desloratadine at pharmacologic concentrations, reaching a maximum of 36% (±8%) at 10 μM (Fig. 2).

Second, at the same concentration, desloratadine also induced maximal inhibition (27% ± 5%) of TNF-α-stimulated adhesion of ^{51} Cr-labeled eosinophils to HUVECs, an effect that was also significantly dose related (Fig. 2).

Third, incubation of eosinophils with desloratadine (10 μM) elicited significant declines (as compared with

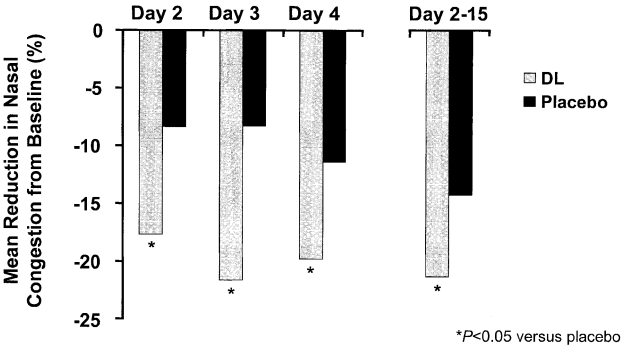

Figure 4. Percent change from baseline in nasal congestion scores for desloratadine 5 mg and placebo. With permission of Prenner et al. (21).

buffer) in both spontaneous and PMA-stimulated generation of superoxide radicals (Fig. 2). These species are toxic to microorganisms invading the upper airway and can also cause tissue damage in SAR. Other potentially toxic granule proteins released by eosinophils during SAR include eosinophil-derived neurotoxin, major basic protein, and eosinophil cationic protein (7).

Effects of desloratadine on SAR-associated nasal congestion

In clinical trials involving patients with moderate-to-severe SAR, desloratadine conferred rapid, sustained relief of nasal congestion. Decongestant efficacy was supported by findings from a number of randomized, double-blind, placebo-controlled trials (21–24). All patients had symptomatic SAR at baseline (pollen season), a minimum 2-year history of pollinosis, a positive skin-test response to a seasonal allergen within the prior year, a minimum age of 12 years, and no nasal structural abnormalities. During a 3- to 4-day baseline run-in and at the study end point, patients rated the severity of nasal congestion/stuffiness symptoms on a 4-point scale (0: none, 3: severe) at 12-h intervals (AM/PM).

The first assessment prior to the morning dose provided an instantaneous rating, which is an excellent measure of the efficacy at the end of the dosing interval, where some agents may lack full therapeutic impact. The two (AM/PM) reflective daily ratings, which involved recall of symptom severity during the prior 12 h, were averaged, and the percent change in mean nasal-congestion symptom severity scores from baseline was the principal outcome variable.

Active-treatment and placebo control arms were well balanced at entry in each trial, with approximate mean baseline nasal-congestion/stuffiness scores of 2.2–2.4, SAR history of 18 years, and a mean age of about 35 years. Desloratadine treatment (5 mg q.d. AM) significantly diminished mean nasal congestion scores (as compared with placebo) within hours after the first dose, and the decongestant effect was maintained through the study end point: days 15–28 in various trials.

Using a Vienna challenge chamber to assess the effects of desloratadine (5 mg q.d.) on allergen-induced SAR symptoms, Horak et al. (25) reported a median time to total SAR symptom relief of 48.5 min, which was consistent with a prompt first-dose effect. All 28 subjects, who were exposed to allergen for 4 h on days 1 and 4 of desloratadine dosing, exhibited a minimum of 25% reduction from baseline in the total symptom severity scores within 160 min, and 19 (68%) of 28 patients responded within 60 min. Finally, patients with at least a 2-point fall in the total symptom severity score from baseline experienced decreases (as compared with baseline) in mean nasal stuffiness scores of nearly 10% at 10 min, approximately 22% at 20–30 min, about 40% at 60 min, and nearly 50% at 90–120 min (Fig. 3) (25).

Furthermore, significantly more pronounced desloratadine-induced declines from baseline in the mean congestion score (as compared with placebo) at treatment days 2 and 15 were noted in a multicenter trial conducted by Prenner et al. (21) (Fig. 4). Similarly, in a pooled-data analysis of SAR patients, desloratadine treatment significantly diminished the severity of nasal stuffiness from baseline at 2 weeks as compared with placebo ($P \leq 0.02$); significant decongestant effects were observed at daily doses of desloratadine ranging from 5 to 7.5 mg q.d. (24).

Desloratadine therapy also relieved nasal congestion when administered to patients with concurrent SAR and asthma (23). In 613 individuals with a 2-year history of AR-asthma, percent reductions from baseline in mean reflective total symptom scores were significantly greater in desloratadine-treated patients than in the control group over weeks 1–2 and 1–4 ($P \leq 0.002$). A significant decongestant effect was evident as early as 12 h after the first dose (23).

Finally, in all desloratadine trials involving nasal congestion in SAR (and SAR-asthma), the agent was well tolerated, exhibiting no anticholinergic or sedative effects and incidences of adverse events similar to those seen with placebo. No clinically significant abnormalities were reported on electrocardiographic parameters (e.g., QT_c interval) or laboratory profiles, and vital signs were similarly unaltered. No dose-related rise in either the incidence or severity of untoward effects was evident when desloratadine was administered at 5–7.5 mg q.d.

In studies to date, desloratadine is the only antiallergy H_1 antagonist with proven, consistent decongestant efficacy on once-daily dosing, alleviating moderate-to-severe nasal congestion in patients with SAR or SAR-asthma within minutes to hours after the first dose and for up to 4 weeks thereafter. In contrast, similarly conducted double-blind, placebo-controlled, randomized trials with other antihistamines, such as cetirizine (5–10 mg q.d.), failed to show comparable decongestant effects (26, 27).

The effects of fexofenadine on nasal congestion have not been assessed systematically. Where clinical trial data are available (26, 28, 29), changes in nasal congestion from baseline did not comprise predefined primary outcome variables, and fexofenadine's decongestant effects were inconsistent. In one study (29), fexofenadine treatment for SAR led to significant decongestant effects (as compared with placebo) after 2 weeks at 120 mg q.d., but not 180 mg q.d. Finally, neither cetirizine nor fexofenadine therapy has shown significant decongestant effects from baseline (as compared with placebo) within hours of the first dose.

Potential clinical implications

The high prevalence of nasal congestion, together with its adverse effect on quality of life, place desloratadine's consistent, sustained decongestant effects in appropriate clinical perspective. At least one 14-day bout with nasal congestion in the prior year was reported in about 17% of questionnaires in a British household survey (30). Furthermore, according to one estimate (31), 47–64% of SAR or PAR subjects suffer from nasal obstruction.

Patients with nasal congestion due to AR are nearly twice as likely to report sleep-disordered respiration (32), and such nighttime symptoms render allergy sufferers significantly more likely to report daytime sleepiness. This problem is of untold dimensions because many patients ascribe their daytime somnolence to medication side-effects. In clinical trials, desloratadine consistently diminished mean nasal congestion symptom severity scores from about 2.3, which was within the range associated with sleep disorders.

The potential physiologic benefits of desloratadine's decongestant effects are at least twofold. First, mucosal swelling and inflammation could conceivably limit the access of other medications to absorptive mucosal surface area and, if severe, could even limit the bioavailability of these agents (33). Second, and perhaps more important, patients suffering from nasal congestion may be more prone to mouth breathing, which can, in turn, promote inhalation of airborne allergens – with introduction of these allergens to the lower airway. These events may contribute to the pathogenesis of AR in certain susceptible individuals (34).

Conclusions

In summary, increasing recognition of the complex interactions in the allergic cascade has prompted a new concept in which the mechanisms of allergy are viewed as aspects of a systemic condition with local, frequently comorbid, tissue effects. In the clinical management of SAR, this approach opens a number of potential lines of therapeutic attack on mediators in the allergic cascade. The novel, nonsedating histamine H_1-receptor antagonist, desloratadine, potentially inhibits the allergic cascade at various points, including both early- and late-phase responses. Furthermore, only desloratadine has shown consistent, significant 24-h decongestant effects with an onset in minutes to hours of the first dose and persisting with daily dosing for up to 4 weeks.

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