

## Introduction

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The past decade has witnessed great advances in the study and treatment of allergic disorders, including seasonal allergic rhinitis (SAR), which is frequently accompanied by, and may share pathogenic foundations with other allergic diseases, including asthma. The advent or refinement of immunohistochemical and other experimental methods has enabled researchers to characterize more accurately the complex immune effector mechanisms underlying allergic signs and symptoms, from the nasal congestion and rhinorrhea of SAR to the wheal of chronic urticaria.

Elucidation of the precise pathophysiologic roles of immune effector cells and proinflammatory mediators in the allergic cascade has prompted a fundamental paradigm shift in our understanding of allergic diseases. The long-standing concept of allergic symptoms as tissue responses to local allergens is now giving way to a view of these conditions as systemic inflammatory processes with local tissue manifestations.

This emerging approach opens multiple avenues for therapeutic intervention, whether through the attenuation of histamine release by submucosal mast cells during the early-phase response of SAR or down-regulation of both proliferation and infiltration of key effector cells (e.g., eosinophils,  $T_H2$  lymphocytes, basophils) during the late-phase-response that could otherwise cause persistence of symptoms and possibly involvement of the lower-airways with appearance of frank asthma. Effective therapeutic attack at multiple loci within the allergic cascade represents a promising strategy for the treatment of patients with SAR, asthma, allergic asthma, or chronic urticaria. Such concerted pharmacologic interventions will be greeted by many allergists with renewed enthusiasm in view of their abilities to enhance the quality of life experienced by patients with these and other chronic allergic conditions.

Also consistent with renascent clinical enthusiasm on the part of allergists is the recent advance from older, first-generation  $H_1$  antihistamines, which had consider-

able untoward central-nervous-system (CNS) effects and short half-lives that necessitated multiple daily dosing, to second-generation, once-daily medications with improved safety and tolerability profiles.

In patients with allergy, however, there remains a clear imperative for further therapeutic progress. Stewards of these patients' care appreciate the upward spiral in the prevalences of certain allergic conditions and the documented links between allergic rhinitis and asthma, as well as the frequent requests for rapidly acting antiallergic therapies that confer broader therapeutic coverage, both across a wider range of symptoms and over a sustained, 24-h dosing interval. This latter need is particularly acute among patients whose daytime functional status is impaired in the wake of persistent nocturnal symptoms.

The four papers in this supplement were developed to highlight an exciting new therapy that promises to meet the foregoing needs. They show that once daily dosing with desloratadine, a novel, nonsedating histamine  $H_1$ -receptor antagonist that modulates several immune effector pathways within the allergic cascade, confers prompt, first-dose relief of a broad array of allergic symptoms. In multicenter, randomized, double-blind, placebo-controlled trials involving patients with SAR, allergic asthma, or chronic idiopathic urticaria (CIU), desloratadine treatment significantly decreased symptoms from baseline throughout the 24-h dosing interval and for up to 6 weeks with continued once-daily dosing.

It is of particular importance that desloratadine showed demonstrable clinical effects that have not been documented consistently with other antihistamines, including second-generation  $H_1$ -receptor antagonists. In placebo-controlled clinical trials, treatment with desloratadine at a daily dosage of 5 mg significantly diminished nasal congestion, as well as other familiar SAR symptoms, in patients with SAR and/or asthma within minutes to hours after the first morning dose;

significantly blunted  $\beta_2$ -agonist use for symptom control in patients with allergic asthma; and also significantly reduced total asthma symptom scores, while maintaining pulmonary function, in patients with concurrent SAR and asthma,

Whether the foregoing clinical benefits can be ascribed directly to desloratadine's inhibitory effects on numerous pathways within the allergic cascade is still unclear. However, desloratadine binds to histamine  $H_1$  receptors with among the highest affinities of antihistamines developed to date: orders of magnitude more avidly than other available medications.

This potent, highly selective  $H_1$ -receptor binding is potentially augmented by other anti-inflammatory actions, which essentially bridge early- and late-phase allergic responses. In various cell lines, exposure to desloratadine significantly suppressed the release by mast cells of histamine as well as the secretion, by various effector cells, of proinflammatory eicosanoids and leukotrienes; cytokines, including interleukins, tumor necrosis factor- $\alpha$ , and granulocyte-macrophage colony stimulating factor; chemokines, including eotaxin and RANTES; and adhesion molecules, including intercellular adhesion molecule-1 and selectins, which promote leukocyte interactions with, and migration across, the vascular endothelium. *In vitro* exposure of eosinophils to desloratadine at pharmacologic concentrations also blunted chemotaxis, adhesion, and superoxide ion generation by these effector cells.

Safe and well tolerated in multicenter clinical trials involving healthy volunteers, as well as patients with SAR, allergic asthma, or CIU, desloratadine treatment was accompanied by low incidences of treatment-emergent adverse events, differences in which were not statistically significant in actively treated patients or placebo controls.

Furthermore, desloratadine treatment caused no untoward CNS or neurobehavioral effects, such as sedation or motor impairment; did not induce QTc prolongation or other adverse electrocardiographic effects (or torsade de pointes); did not accumulate when coadministered with certain cytochrome P450 3A4 inhibitors; exhibited consistent, predictable pharmacologic effects irrespective of patient race or sex; and could be taken with food or grapefruit juice without changes in absorption or bioavailability.

In summary, the articles reported in this Allergy Supplement call attention on desloratadine is a novel, nonsedating histamine  $H_1$ -receptor antagonist with diverse effects on the allergic cascade. Administered once daily, desloratadine confers rapid antiallergic effects in SAR, asthma, allergic asthma, and CIU that are sustained over a 24-h dosing interval. Perhaps because of its broad-spectrum anti-inflammatory activities, desloratadine imparts consistent decongestant and antiasthmatic effects that are considered unprecedented among antihistamines. Both safe and well tolerated, desloratadine thus represents a major potent tool in the pharmacopeia for these allergic conditions.