

Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis

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Background: The evidence base for the use of H₁-antihistamines in the treatment of perennial allergic rhinitis is considerably smaller than it is in the treatment of seasonal allergic rhinitis.

Objective: We hypothesized that desloratadine, a new, non-sedating selective H₁-antihistamine, would be efficacious and safe in the treatment of perennial allergic rhinitis.

Methods: In a multicenter, randomized, placebo-controlled, double-blind, parallel-group study, 676 patients with symptomatic perennial allergic rhinitis were randomly assigned to 4 weeks of treatment with either 5 mg of desloratadine once daily or placebo. Efficacy was assessed by using a morning-evening instantaneous total symptom score (TSS), which was composed of scores for 4 individual nasal symptoms (rhinorrhea, itching, sneezing, and postnasal drip) and 3 individual nonnasal symptoms (itching eyes, watering eyes, and itching of the ears or palate). Secondary outcome measures included a morning-evening reflective TSS, total nasal and nonnasal symptoms scores, and individual symptom scores. Safety evaluations, including 12-lead electrocardiograms, were performed.

Results: Six hundred thirty-four patients completed the study. Desloratadine consistently diminished perennial allergic rhinitis symptoms, reducing the morning-evening instantaneous TSS ($P = .005$), the morning-evening reflective TSS ($P = .007$), the morning-evening reflective total nonnasal score ($P = .023$), and the individual nasal symptom scores for rhinorrhea, nasal itching, sneezing, and postnasal drip/drainage ($P = .05$ to $P = .013$) during weeks 1 through 4. Improvement in symptoms was observed after the first dose. Dropouts, and the type and frequency of adverse events (headache, viral infection, pharyngitis, and upper respiratory tract infection), were similar in both treatment groups. No clinically significant changes in QTc intervals were observed.

Conclusions: Desloratadine rapidly and safely reduced the

symptoms of perennial allergic rhinitis, and its efficacy did not diminish during 4 weeks of treatment. (*J Allergy Clin Immunol* 2003;111:617-22.)

Key words: Desloratadine, H₁-antihistamine, perennial allergic rhinitis, persistent allergic rhinitis

Perennial allergic rhinitis affects up to 21% of the general population in some countries.¹ In temperate climates house dust mite, cockroach, mold, and animal dander are common allergens triggering perennial allergic rhinitis symptoms. In subtropical or tropical climates, pollen might also trigger perennial symptoms.^{2,3}

Allergic rhinitis is characterized by inflammation of the nasal mucosa involving activation of CD4⁺ T cells, Langerhan's cells, mast cells, epithelial cells, and endothelial cells and recruitment and activation of eosinophils and basophils. Macrophages, neutrophils, and fibroblasts also play a role. The allergic response is characterized by the synthesis and release of T_H2 cytokines and the coordinate expression of chemokines and adhesion molecules.⁴ The end-organ effects of nasal itching, sneezing, rhinorrhea, and congestion, as well as itching of the eyes, nose, and palate, occur as a result of release of chemical mediators of inflammation, including histamine, leukotrienes and other arachidonic acid metabolites, and kinins from activated effector cells, primarily mast cells and basophils. Histamine plays an important role in the pathophysiology of allergic rhinitis through its neural and vascular effects, leading to itching, sneezing, rhinorrhea, and congestion, and also through its proinflammatory effects, including increased expression of adhesion molecules, cytokines, and chemokines.⁴

H₁-antihistamines are recommended as first-line treatment in perennial allergic rhinitis^{2,3}; however, they have not been optimally studied in this disorder. In contrast, in seasonal allergic rhinitis the evidence base for their efficacy consists of hundreds of prospective, randomized, placebo-controlled, double-blind, parallel-group studies.^{2,3,5} Desloratadine, a new oral selective H₁-antihistamine with anti-inflammatory and anti-allergic activities in addition to its antihistaminic activity has a 27-hour elimination half-life, which facilitates once daily dosing. In clinical pharmacology and seasonal allergic rhinitis studies to date, its adverse event profile has been similar to that of placebo.⁶⁻¹¹ We hypothesized that desloratadine would be more effective than placebo in decreasing the symptoms of perennial allergic rhinitis.

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Supported by Schering-Plough, Kenilworth, NJ.

Received for publication July 12, 2002; revised November 14, 2002; accepted for publication November 26, 2002.

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0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.168

TABLE I. Severity score for individual signs and symptoms of perennial allergic rhinitis

Severity score	
0 = none	No signs or symptoms present
1 = mild	Signs/symptoms clearly present but minimal awareness of them; tolerable
2 = moderate	Clear awareness of signs/symptoms; bothersome but tolerable
3 = severe	Signs/symptoms difficult to tolerate; might cause interference with activities of daily living, sleeping, or both

Abbreviation used

TSS: Total symptom score

METHODS**Study design**

This randomized, placebo-controlled, double-blind, parallel-group study was approved by the institutional review board of each participating center. All patients provided written informed consent before study entry. During the screening evaluation, which was conducted 4 to 14 days before randomization, inclusion and exclusion criteria were assessed, medical history was obtained, physical examination was conducted, and severity of allergic rhinitis was determined. A 12-lead electrocardiogram and laboratory tests (hematology and blood chemistry tests and urinalysis) were performed. After screening, participants were assigned to 4 weeks of treatment with 5 mg of desloratadine once daily or placebo by using a computer-generated randomization schedule. Study visits were conducted at screening, baseline (day 1), and days 8, 15, and 29.

Inclusion and exclusion criteria

Patients were considered for study inclusion if they were 12 years of age or older, had a history of moderate perennial allergic rhinitis symptoms of at least 2 years' duration, and had a positive skin test response to 1 or more allergens (house dust mite, cockroach, mold, and animal dander) within the previous 12 months. At the screening visit, they were required to have perennial allergic rhinitis symptoms with a 12-hour reflective total symptom score (TSS), including nasal stuffiness-congestion, of at least 10 (maximum score, 24) and no greater than moderate nasal stuffiness/congestion (see Efficacy evaluations). The summed reflective score for congestion during the 3 days before baseline was required to be no greater than 12, and the summed TSS was required to be at least 60 (see Efficacy evaluations). The overall rhinitis score at baseline was required to be greater than 2 (on the basis of a 4-point scale), indicating moderate-to-severe disease.

Patients were required to be in good general health, as confirmed by history, physical examination, hematology and blood chemistry tests, and urinalysis. Women of childbearing potential were required to have a negative serum pregnancy test at screening and to use a medically accepted method of contraception before screening and during the study.

Exclusion criteria included: seasonal allergic rhinitis triggered by an allergen pollinating during the time of the study, structural abnormalities interfering with nasal airflow, an upper respiratory tract or sinus infection requiring antibiotic treatment within 14 days before screening, a viral upper respiratory tract infection during the 7 days before screening, and current or past history of recurrent or chronic sinusitis, chronic purulent postnasal drip, rhinitis medicamentosa, or asthma that necessitated the regular use of inhaled corticosteroids or use of systemic corticosteroids. Also excluded were patients with a history of adverse reactions to more than 2 classes of medications or those with a history of adverse effects to antihistamines. Patients who had used any investigational drug in the 30

days before screening, as well as those judged to be dependent on decongestants (nasal, oral, or ocular), intranasal H₁-antihistamines, or intranasal corticosteroids, were also excluded in the interest of safety. Medications prohibited during the study included cromolyn, nedocromil, corticosteroids (other than low- or moderate-potency dermatologic preparations), H₁-antihistamines other than desloratadine (including topical ketotifen or levocabastine), leukotriene modifiers, intranasal ipratropium bromide, ocular or intranasal saline, or systemic antibiotics. Pseudoephedrine was permitted on an as-needed basis for use as a rescue medication for relief of severe congestion. Appropriate washout times were required for previous use of prohibited medications.

Patients receiving allergen immunotherapy were excluded unless they were on a regular maintenance schedule before screening and could maintain this schedule for the duration of the study; however, desensitization treatment within 24 hours before a study visit was prohibited. Pregnant or nursing women were also excluded.

Study medications

The 5-mg desloratadine tablets were identical in appearance to the placebo tablets and were packaged identically. All study personnel were blinded to the identity of the tablets, which were distributed in sealed and coded bottles. Participants were instructed to take each dose of study medication in the morning at approximately the same time each day. Compliance was assessed on the basis of diary card review, direct questioning, and tablet counts. As noted previously, participants were permitted to take pseudoephedrine for treatment of severe nasal congestion, and nasal congestion was therefore excluded from the primary TSS efficacy analyses.

Efficacy evaluations

Allergic rhinitis severity was assessed by using symptom scores recorded on daily diary cards. Symptoms of perennial allergic rhinitis (ie, rhinorrhea, nasal itching, sneezing, postnasal drip/drainage, itchy/burning eyes, tearing/watering eyes, and itching of ears or palate) were individually assessed by using a 4-point scale (0 = none to 3 = severe, Table I). The TSS was the sum of the 4 nasal symptoms (rhinorrhea, nasal itching, sneezing, and postnasal drip/drainage) and 3 nonnasal symptoms (itchy/burning eyes, tearing/watering eyes, and itching of the ears or palate). Congestion, although an important inclusion criterion and a symptom that was scored during this study, was not included in the TSS because patients could use pseudoephedrine as needed. Participants, their parents or guardians, or both scored the severity of perennial allergic rhinitis symptoms twice daily on the basis of how they felt during the previous 12 hours (reflective) and how they felt at the time of assessment (instantaneous). The symptoms were scored and recorded on awakening (predose) and approximately 12 hours later. The morning instantaneous evaluations provided an assessment of the duration of the treatment.

The overall severity of allergic rhinitis was assessed jointly by investigators and participants at baseline and at subsequent visits by using a 4-point scale (0 = none to 3 = severe). The overall response to study medication was also assessed jointly by the investigators and participants at each postbaseline visit by using a 5-point scale (1 = complete relief to 5 = treatment failure).

Efficacy variables

The primary efficacy outcome was the 4-week average morning-evening instantaneous TSS expressed as a change from baseline. Secondary outcomes included morning-evening reflective TSS, total nasal symptom score, total nonnasal symptom score, and each of the 7 individual symptom scores. Overall condition and therapeutic response were measured at each study visit and were expressed as change from baseline and as raw scores. All efficacy analyses were performed by using the intent-to-treat data.

Safety evaluations

Vital signs and adverse events were assessed at each study visit. All adverse events were graded according to severity and the potential relationship to study medication. Blood chemistry and hematology tests, urinalysis, and 12-lead electrocardiograms with reporting of ventricular rate and PR, QRS, QT and QTc intervals were performed at screening and at the end of the study.

Statistical analysis

The sample size of 300 participants per treatment group was chosen to detect, with 90% power and at a 5% significance level, a difference between desloratadine and placebo of 1.3 units or more in the mean TSS expressed as a change from baseline, assuming a pooled SD of 5.0. All randomized participants who had at least 1 postrandomization evaluation were included in the data analysis. The primary variable, the 4-week average morning-evening instantaneous TSS expressed as a change from baseline, was analyzed by using a 2-way ANOVA model that extracted sources of variation caused by treatment and center. The secondary variables expressed as a change from baseline were analyzed for the average over the 4-week treatment period, the first 4 days of treatment, and the average over each of weeks 1 through 4. All secondary variables were analyzed by using a 2-way ANOVA model that extracted sources of variation caused by treatment and center.

RESULTS

Dropouts and baseline demographics

A total of 676 participants were randomized to treatment at 33 centers: 337 to desloratadine and 339 to placebo. Twenty (5.93%) participants randomized to desloratadine and 22 (6.48%) randomized to placebo did not complete the study. The reasons for early discontinuation were similar between the groups. Discontinuations as a result of lack of efficacy occurred in 6% and 7% of patients in the desloratadine and placebo groups, respectively. Discontinuations as a result of adverse events occurred in 3.3% and 2.1% of patients in the desloratadine and placebo groups, respectively. In the desloratadine group these events included sinusitis, asthma, upper respiratory tract infection, nausea, headache, gingivitis, and fracture. In the placebo group they included sinusitis, cough, upper respiratory tract infection, dizziness/asthenia, and benign palate cyst.

The groups had similar baseline characteristics (Table II). The majority of participants were white, and more women than men were enrolled. At baseline, the mean morning-evening instantaneous TSS did not differ in the desloratadine (10.70) and placebo groups (10.64).

Efficacy

During days 1 through 29, desloratadine was significantly more effective than placebo for reducing the

TABLE II. Baseline demographics

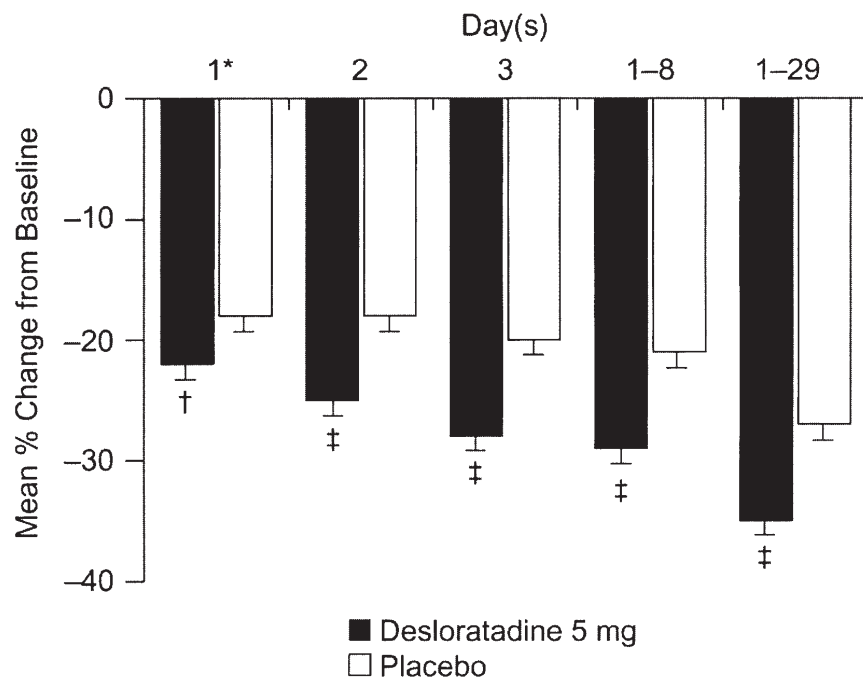
	Desloratadine (n = 337)	Placebo (n = 339)
Sex, n (%)		
Women	229 (68)	248 (73)
Men	108 (32)	91 (27)
Race, n (%)		
White	275 (82)	279 (82)
Black	19 (6)	24 (7)
Asian	6 (2)	5 (1)
Hispanic	34 (10)	28 (8)
Other	3 (<1)	3 (<1)
Mean age, y (range)	34.7 (12-68)	34.8 (11-79)
Age subgroup, n (%)		
12 to <18 y	29 (9)	28 (8)
18 to <65 y	305 (91)	300 (88)
≥65 y	3 (<1)	10 (3)

morning-evening instantaneous TSS, with mean reductions from baseline of 35.0% with desloratadine and 27.4% with placebo ($P = .005$, Fig 1). A significant difference ($P = .001$) between groups was noted after the first dose at the first time point for which complete 24-hour data were available (day 2), and this difference persisted for the duration of the study. A supplemental analysis of instantaneous TSS that included nasal congestion provided similar results to those reported for the primary outcome (TSS minus nasal congestion). At days 1 through 29, there was a significant improvement from baseline values in mean instantaneous TSSs compared with placebo ($P = .006$); mean percentage reductions from baseline were 30.8% and 23.8% for the desloratadine and placebo groups, respectively. Desloratadine was more effective than placebo as early as day 1 and continued throughout the treatment period.

The mean change from baseline in morning-evening reflective TSS over days 1 through 29 was significantly greater in the desloratadine group than in the placebo group (-37.9% vs -32.3% , respectively; $P = .007$). Desloratadine was significantly more effective than placebo in reducing mean morning-evening reflective TSSs at most time points ($P \leq .018$).

Desloratadine was associated with significantly greater improvements in both instantaneous and reflective ($P \leq .005$, Fig 2) total nasal symptom scores during days 1 through 29. Mean percentage reductions in morning-evening reflective total nonnasal symptom scores during days 1 through 29 were significantly greater with desloratadine than with placebo ($P = .023$, data not shown).

Statistically significant improvements from baseline in mean morning-evening instantaneous individual symptom scores (Fig 3) compared with placebo were observed for rhinorrhea, nasal itching, sneezing, and postnasal drip/drainage, but not for nasal congestion, at the primary time point (days 1-29). The results of the mean morning-evening reflective, morning instantaneous, morning reflective, evening instantaneous, and evening reflective individual symptom score analyses were similar to those of the morning-evening instantaneous analysis.

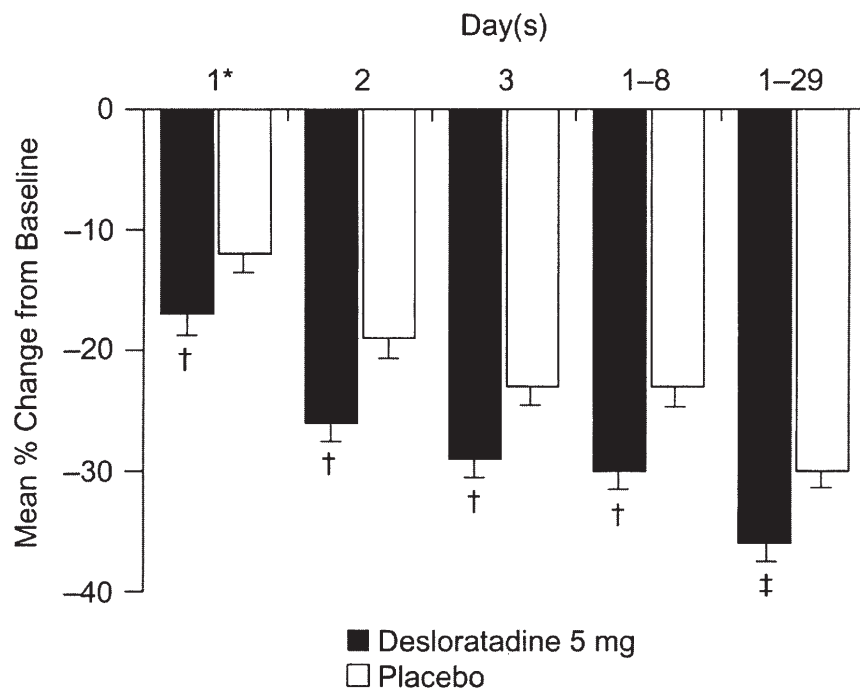


*Day 1 includes evening scores only

[†] $P < .057$ compared with placebo

[‡] $P \leq .005$ compared with placebo

FIG 1. Mean percentage reduction in the 4-week average morning-evening instantaneous TSSs. Baseline values were 10.7 and 10.6 for the desloratadine- and placebo-treated groups, respectively.



*Day 1 includes evening scores only

[†] $P \leq .017$ compared with placebo

[‡] $P < .01$ compared with placebo

FIG 2. Mean percentage reduction in the 4-week average morning-evening reflective total nasal symptom scores. Baseline value was 7.0 in both the desloratadine- and placebo-treated groups.

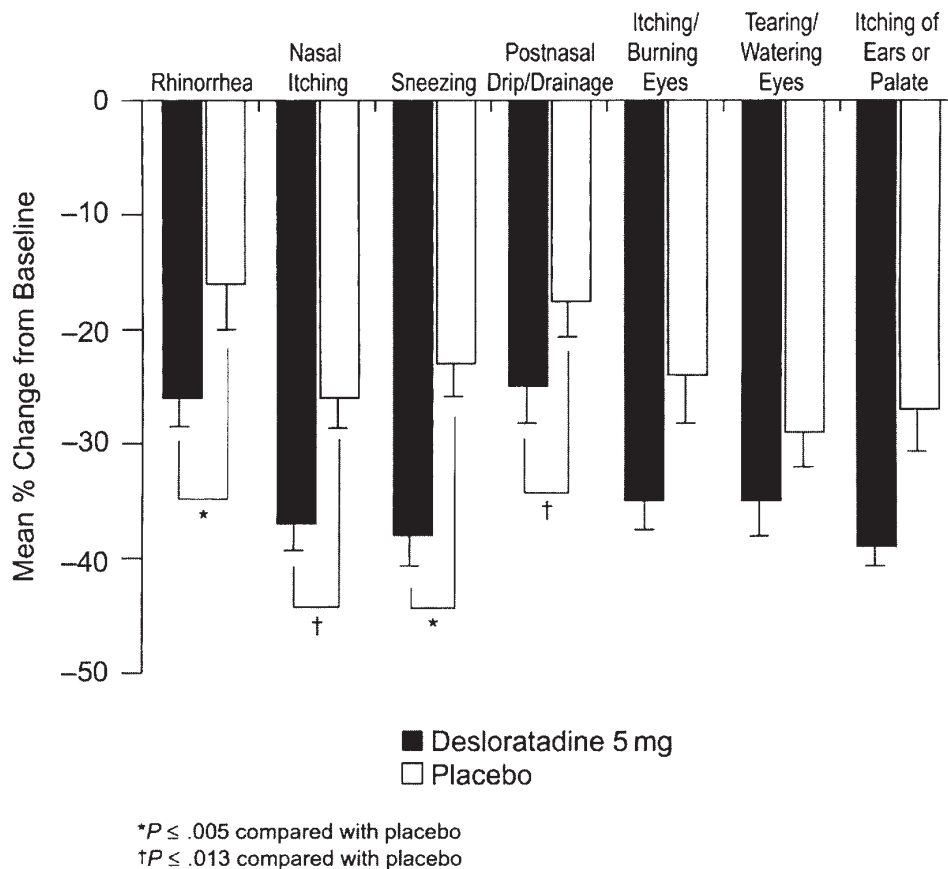


FIG 3. Mean percentage reduction in morning-evening instantaneous individual nasal symptom scores over days 1 through 29. Baseline values in both the desloratadine- and placebo-treated groups were as follows: rhinorrhea, 1.8; nasal itching, 1.6; postnasal drip/drainage, 1.8; itching/burning eyes, 1.5; tearing/watering eyes, 1.3; and itching of ears or palate, 1.3. For sneezing, the baseline values were 1.4 in the desloratadine-treated group and 1.5 in the placebo-treated group.

In terms of overall therapeutic response, desloratadine was significantly more effective than placebo at end point ($P < .001$) and at all other evaluation visits (all $P \leq .009$).

Safety

Treatment-emergent adverse events (Table III) occurred in 25.8% of desloratadine-treated participants and in 31.6% of placebo-treated participants. The type and frequency of adverse events were similar in both treatment groups. The most commonly reported adverse events in both the desloratadine and the placebo groups were headache (7.4% and 7.1%, respectively), viral infection (3.3% and 5.3%, respectively), pharyngitis (3.0% and 1.5%, respectively), and upper respiratory tract infections (2.7% in both treatment groups). Most adverse events were mild or moderate in severity. No deaths occurred, and there were no serious or unexpected adverse events reported that were attributable to desloratadine therapy.

There was no difference in early discontinuation of treatment as a result of adverse events between the desloratadine and placebo groups (3.3% and 2.1%, respectively). Most adverse events leading to early discontinuation were moderate in severity, and the investigators consid-

TABLE III. Incidence of treatment-emergent adverse events reported for 2% or more of the participants

Symptoms/signs	No. (%) of participants	
	Desloratadine (n = 337)	Placebo (n = 339)
Headache	25 (7.4)	24 (7.1)
Infection, viral	11 (3.3)	18 (5.3)
Pharyngitis	10 (3.0)	5 (1.5)
Upper respiratory tract infection	9 (2.7)	9 (2.7)
Dry mouth	8 (2.4)	6 (1.8)

ered them unlikely to be related to treatment with desloratadine or placebo. The most common adverse events leading to early discontinuation were related to viral upper respiratory tract infections.

No clinically significant differences in vital signs, clinical laboratory test results, or electrocardiograms, including QTc intervals, were observed compared with baseline values or between the desloratadine- and placebo-treated groups.

DISCUSSION

In the present study, which was conducted in adolescents and adults, we have demonstrated that once daily administration of desloratadine relieved the symptoms of rhinorrhea, nasal itching, sneezing, and postnasal drip-drainage significantly in patients with perennial allergic rhinitis, thus adding to the small body of evidence currently supporting the use of H₁-antihistamines in this disorder. The major limitation in this study was our patients' unrestricted use of pseudoephedrine for rescue treatment of nasal congestion, and this is likely reflected in the lack of a statistically significant difference in the individual symptom scores for congestion.

Desloratadine treatment was associated with significant reductions in the TSS, as well as in the total nasal and nonnasal symptom scores. It had a rapid onset of action, providing significant relief after the first dose. Efficacy was maintained throughout the 24-hour dosing interval and did not wane during 4 weeks of treatment. Desloratadine was well tolerated, with no evidence of sedation or cardiac toxicity. The results of this study in patients with perennial allergic rhinitis are consistent with the results of previous studies of desloratadine in patients with seasonal allergic rhinitis, in which it provided rapid and sustained relief of rhinitis symptoms and was well tolerated.⁹⁻¹¹

In contrast to the large numbers of studies on seasonal allergic rhinitis, there are very few published studies of the efficacy and safety of H₁-antihistamines in perennial allergic rhinitis. In randomized, double-blind, placebo-controlled trials, azelastine,¹² cetirizine,¹³⁻¹⁵ ebastine,^{14,16,17} fexofenadine,¹⁸ loratadine,¹⁹⁻²¹ and mizolastine^{21,22} have been reported to improve perennial allergic rhinitis symptoms; however, of these medications, only cetirizine and desloratadine are approved for the treatment of perennial allergic rhinitis in the United States.

In the future, controlled clinical trials in which desloratadine is directly compared with other H₁-antihistamines will further define its place in perennial allergic rhinitis management. In the present study, as in virtually all previous clinical trials in patients with either seasonal or perennial allergic rhinitis, traditional subjective assessments of rhinitis symptoms were used to evaluate the efficacy of the interventions. In subsequent studies, objective measurements should be incorporated wherever possible; for example, nasal peak inspiratory flow, which is easily performed and correlates with subjective assessment of nasal congestion,²³ has, to date, been underused in large clinical trials.

In summary, desloratadine is effective and safe in the treatment of perennial allergic rhinitis. It rapidly reduces nasal and nonnasal symptoms, and its effects do not diminish during 4 weeks of treatment.

We gratefully acknowledge the assistance of all of the physicians in the Desloratadine Study Group.

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