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# Desloratadine therapy for symptoms associated with perennial allergic rhinitis

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**Background:** Perennial allergic rhinitis (PAR) has a substantial negative social and economic impact. Recent studies emphasize the potential seriousness of PAR and the need for improved treatment of this condition.

**Objective:** To confirm the efficacy and safety of the H<sub>1</sub>-antihistamine desloratadine in reducing the symptoms of PAR in a randomized, double-blind, placebo-controlled trial.

**Methods:** Patients with PAR (N = 1,179) from 67 US/international centers received desloratadine, 5 mg once daily, or identical placebo tablets. The primary efficacy measure was the change from baseline to week 4 in average morning and evening reflective total symptom scores (TSSs). Secondary end points included changes from baseline in total nasal and nonnasal symptom scores and peak nasal inspiratory flow (PNIF) rates.

**Results:** Desloratadine was significantly more effective than placebo in reducing morning and evening reflective TSSs for each week and during weeks 1 through 4 ( $P = .001$ ). Mean changes in TSSs during the 4-week study were  $-3.9$  (26.6% reduction) and  $-3.2$  (22.3% reduction) for the desloratadine and placebo groups, respectively ( $P = .001$ , desloratadine vs placebo). With desloratadine therapy, significant improvements were also seen in secondary efficacy end points compared with placebo use (total nasal and nonnasal symptom scores:  $P \leq .04$ ). Improvements in mean morning PNIF were significantly greater in the desloratadine-treated group than in the placebo group ( $P = .03$ ).

**Conclusions:** These results confirm and extend previous findings that desloratadine is safe and is associated with a statistically significant reduction in nasal and nonnasal symptoms in patients with PAR. Objective nasal airflow, evaluated by PNIF, was statistically significantly improved after desloratadine treatment.

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## INTRODUCTION

The annual incidence of allergic rhinitis (AR) is increasing globally. In addition to the physical symptoms experienced by individuals with this disease, AR contributes to substantial losses in school and workplace productivity. Recently, several research groups<sup>1,2</sup> addressed the economic implications of AR, and it is estimated that the annual loss of workplace productivity due to AR exceeds \$4.6 billion.<sup>2</sup> Some individuals experience only seasonal occurrence of symptoms; however, perennial signs and symptoms affect up to 21% of the population and are usually caused by allergens such as house dust mites, molds, and animal dander.<sup>3–5</sup> In warmer climates, pollen may also serve as a trigger for symptoms of perennial allergy.

Physicians have begun to recognize that seasonal AR (SAR) and perennial AR (PAR) are separate diseases with dissimilar symptom presentations. Nasal congestion and rhinosinusitis predominate in patients with PAR, and conjunc-

tival itching is less severe. In a recent study, Diemer and colleagues<sup>6</sup> reported the increased seriousness of PAR compared with SAR. These authors suggested that in uncomplicated AR, PAR may be more severe than SAR, owing primarily to the chronicity of the disease. In another study, Scadding and colleagues<sup>7</sup> evaluated patient and physician perspectives on the impact and management of SAR and PAR. Overall, physicians rated PAR as more difficult to treat than SAR. Physicians and patients also reported greater dissatisfaction with currently administered therapies for the symptoms of PAR. Collectively, these results emphasize the potential seriousness of PAR and the need for improved treatment of this chronic condition.

The H<sub>1</sub>-antihistamines have demonstrated efficacy in the treatment of patients with PAR,<sup>8,9</sup> and they remain a first-line therapy for this condition. Results of studies conducted during clinical development show that desloratadine, a once-daily H<sub>1</sub>-receptor antagonist, has favorable effects on nasal congestion in patients with AR.<sup>10–14</sup> More recently, Simons and colleagues<sup>15</sup> reported that desloratadine therapy was more effective than placebo use in alleviating the symptoms of PAR, and their results showed rapid and statistically significant improvement in subjective measures of symptom severity, such as total nasal and nonnasal symptom scores. The present study was undertaken (1) to confirm and extend the results of the previous PAR study<sup>15</sup> by providing subjective and objective measurements and (2) to demonstrate that

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desloratadine is an effective and safe therapy compared with placebo for reducing nasal and nonnasal symptoms associated with this bothersome condition.

## METHODS

### *Study Design*

This randomized, double-blind, placebo-controlled, multicenter study compared the efficacy and safety of desloratadine, 5 mg, with identical placebo tablets administered orally once daily for 4 weeks in patients with PAR at 67 institutions (56 centers in the United States and 11 international centers). The primary efficacy end point was the mean change from baseline in morning and evening reflective total symptom scores (TSSs) averaged for the 4-week study. The TSS is a composite severity score of individual symptoms, including rhinorrhea, nasal congestion or itching, sneezing, itching or burning eyes, tearing or watering eyes, and itching of the ears or palate. Secondary efficacy measures included changes from baseline in the total nasal symptom score (TNSS), total nonnasal symptom score (TNNSS), and peak nasal inspiratory flow (PNIF) rate.

### *Patient Population*

Patients were 12 years or older with a history of PAR for at least 2 years. Patients were required to have a TSS of 9 or greater, a TNSS of 5 or greater, and a TNNSS of 4 or greater at the initial screening visit and a positive skin prick response to an appropriate perennial allergen (eg, dust mites or animal dander) within 12 months of the study. A positive skin prick response was defined as a wheal diameter at least 3 mm greater than that of the diluent control. For intradermal testing, wheal diameter had to be at least 7 mm greater than that of the control. All the patients were required to be in good general health and free of any clinically significant disease that could interfere with the evaluation of study medication. Women were obliged to have a negative serum pregnancy test result at screening and to use a medically acceptable form of birth control throughout the study; women who were pregnant or breastfeeding were excluded from the study.

Patients were excluded from the study if they had any of the following: structural abnormalities that interfered with nasal airflow, a current diagnosis or a history of acute or chronic sinusitis, chronic purulent postnasal drip, rhinitis medicamentosa, asthma that required regular use of systemic or inhaled corticosteroids, or a skin test that demonstrated mold as the only qualifying perennial allergen. Additional exclusion criteria included the use of any investigational drugs within 30 days of screening and dependence on nasal topical antihistamines, nasal corticosteroids, or nasal, oral, or ocular decongestants. Patients receiving immunotherapy were excluded unless they had been taking medication on a regular maintenance schedule before screening and could maintain this schedule for the duration of the study. However, immunotherapy injection 24 hours before a study visit was prohibited to avoid the potential for associated adverse events.

Use of the following medications was prohibited during the study: nasal or ophthalmic cromolyn or nedocromil, corticosteroids (other than low- or moderate-potency dermatologic preparations), H<sub>1</sub>-antihistamines other than desloratadine, leukotriene modifiers, intranasal atropine or ipratropium bromide, ocular or intranasal saline, systemic antibiotics, and nasal, oral, or ocular decongestants. In accordance with the Declaration of Helsinki, an appropriate institutional review board approved the study, and all the patients (and their parents or guardians) provided written informed consent before study participation.

### *Study Procedures*

Patients were evaluated at 5 visits. At visit 1 (the screening visit), nasal and nonnasal symptoms were evaluated. The severity of PAR symptoms, which was evaluated in terms of the patient's status during the preceding 12 hours (reflective) and at the present time (instantaneous), was graded according to a 4-point scale (0 = none present; 1 = signs or symptoms clearly present but minimal awareness and easily tolerated [mild]; 2 = definite awareness of signs or symptoms, bothersome but tolerable [moderate]; and 3 = signs or symptoms difficult to tolerate and may interfere with daily activities or sleeping [severe]). Scores for individual symptoms were then combined to obtain the TSS (rhinorrhea, nasal congestion/itching, sneezing, itching/burning eyes, tearing/watering eyes, and itching of the ears/palate), the TNSS (rhinorrhea, nasal congestion/itching, sneezing), and the TNNSS (itching/burning eyes, tearing/watering eyes, and itching of the ears/palate). In addition, patients and investigators jointly evaluated the overall severity of PAR using the same 4-point scale that had been used to evaluate individual symptom severity. Physical and laboratory examinations (including electrocardiography [ECG]) were also performed during the screening visit, and the patients were instructed regarding the use of a PNIF device. During the subsequent screening period (up to 30 days), patients (or parents/guardians, if appropriate) used the same 4-point scale to record the severity of PAR signs and symptoms in a diary twice daily: once within 1 hour of awakening in the morning and again approximately 12 hours later.

To qualify for study entry, at visit 2 (the baseline visit) patients were required to have a reflective TSS of 63 or greater, a TNSS of 35 or greater, and a TNNSS of 28 or greater during the 3 days before randomization. These scores were based on the morning and evening diary entries for the 3 preceding days and the morning recording on the baseline day. Qualifying patients were randomly assigned to treatment with 5 mg of desloratadine or placebo once daily. Thereafter, patients used diary cards to record the severity of their PAR symptoms twice daily, with assessments defined as reflective or instantaneous. The PNIF measurements also were evaluated twice daily, and all adverse events were recorded.

Additional clinic visits were scheduled for days 8 (visit 3), 15 (visit 4), and 29 (visit 5). At each visit, symptom diary cards were collected, and compliance was reviewed. Patients

and investigators jointly evaluated the overall severity of PAR signs and symptoms, a nasal examination was performed, and vital signs were checked. Response to treatment was graded according to a 5-point scale (1 = complete relief, 2 = marked relief, 3 = moderate relief, 4 = slight relief, and 5 = treatment failure) and was evaluated by patients at study visits 3, 4, and 5. At visit 5, laboratory assessments and an ECG were performed.

### Statistical Methods

With a sample size of 520 patients per treatment group, a between-group difference of approximately 0.8 U or greater was detected in the mean change from baseline, with a power of at least 90% and  $\alpha = .05$ , assuming a pooled SD of 3.9 points. The primary efficacy variable was analyzed by means of linear contrasts of the treatment means, which were obtained from a 2-way analysis of variance model that extracted sources of variation attributed to treatment and study center. All secondary end points were analyzed according to the same analysis of variance model. Summary statistics were calculated for the incidences of treatment-emergent adverse events, discontinuations due to adverse events, and changes in ECG and laboratory variables.

## RESULTS

A total of 1,179 patients were randomly assigned to treatment: 591 patients received 5 mg of desloratadine and 588 received placebo. Of these patients, 1,072 (91%) completed the study. The treatment groups had similar baseline characteristics (Table 1). Most patients were white (83%) and female (66%), with a mean age of 35 years. Mean baseline values for the morning and evening reflective TSSs (including nasal congestion) and the morning and evening PNIF measurements were similar in both groups (Table 2).

The primary efficacy end point was the change from baseline in morning and evening reflective TSSs (including nasal congestion) averaged for the 4-week study. Desloratadine was significantly more effective than placebo in reducing

Table 1. Baseline Demographic Characteristics of the 1,179 Study Participants

Characteristic	Desloratadine, 5 mg group (n = 591)	Placebo group (n = 588)
Age, mean (range), y	35 (12–72)	35 (12–76)
Sex, No. (%)		
F	398 (67)	378 (64)
M	193 (33)	210 (36)
Race, No. (%)		
White	491 (83)	490 (83)
Black	53 (9)	56 (10)
American Indian	1 (<1)	0
Asian	17 (3)	13 (2)
Hispanic	23 (4)	24 (4)
Other	6 (1)	5 (<1)
Height, mean (range), cm	168 (141–203)	169 (142–198)
Weight, mean (range), kg	77 (29–159)	77 (34–181)

Table 2. Baseline Clinical Characteristics of the 1,179 Study Participants\*

Characteristic	Desloratadine, 5 mg group (n = 591)	Placebo group (n = 588)
TSS (including nasal congestion)	14.3	14.2
TNSS	8.5	8.5
TNNSS	5.8	5.7
Overall PAR condition	2.4	2.4
PNIF, L/min		
Morning	92.2	93.9
Evening	96.0	97.3

Abbreviations: PAR, perennial allergic rhinitis; PNIF, peak nasal inspiratory flow; TNNSS, total nonnasal symptom score; TNSS, total nasal symptom score; TSS, total symptom score.

\* Data are given as means.

reflective TSSs: mean reductions from baseline were  $-3.9$  (mean change, 26.6%) and  $-3.2$  (mean change, 22.3%), respectively ( $P = .001$ ) (Fig 1). The mean reduction from baseline in TSSs throughout the entire study was greater in the desloratadine group than in the placebo group, and the difference was significant for all times and intervals beginning with day 2 ( $P \leq .02$ ) (Table 3 and Fig 1).

When mean TNSS and TNNSS were analyzed separately, desloratadine treatment similarly resulted in significantly greater reductions from baseline compared with placebo use. Patients receiving desloratadine experienced a mean reduction from baseline in TNSS of  $-2.1$  (mean change, 23.7%) compared with  $-1.8$  (mean change, 19.8%) in patients receiving placebo ( $P = .004$ ) (Fig 2). Desloratadine was significantly more effective ( $P \leq .04$ ) than placebo in reducing TNSS (including nasal congestion) at all times and intervals

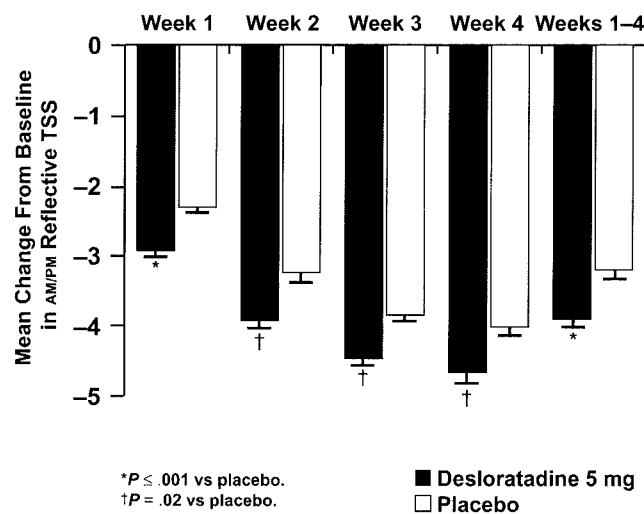


Figure 1. Mean change from baseline in morning/evening (AM/PM) reflective total symptom score (TSS). Mean baseline values were 14.3 and 14.2 for the desloratadine-treated and placebo groups, respectively. Error bars represent SD.

Table 3. Change From Baseline in Symptom Scores on Days 1 to 4

Symptom score	Mean change from baseline		P value
	Desloratadine, 5 mg, group (n = 591)	Placebo group (n = 588)	
TSS (including nasal congestion)			
Day 1*	-1.4	-1.2	NS
Day 2	-2.3	-1.7	.001
Day 3	-2.8	-2.1	.002
Day 4	-2.9	-2.3	.01
TNSS			
Day 1*	-0.7	-0.6	NS
Day 2	-1.2	-0.9	.002
Day 3	-1.5	-1.1	.003
Day 4	-1.5	-1.3	NS
TNNSS			
Day 1*	-0.6	-0.6	NS
Day 2	-1.1	-0.8	.007
Day 3	-1.3	-1.0	.01
Day 4	-1.4	-1.1	.005

Abbreviations: NS, not significant; TNNSS, total nonnasal symptom score; TNSS, total nasal symptom score; TSS, total symptom score. \* Day 1 includes the evening score only.

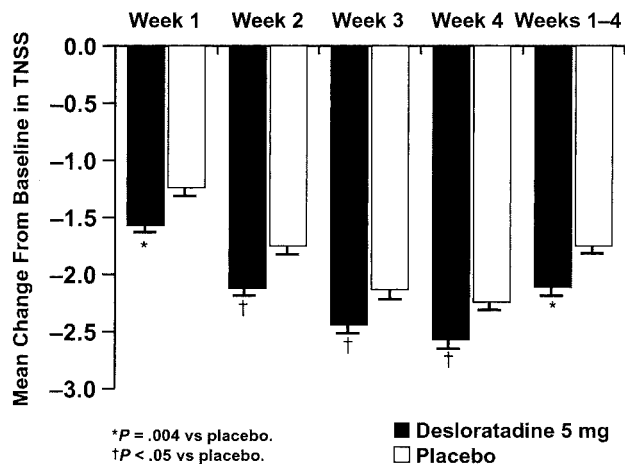


Figure 2. Mean change from baseline in total nasal symptom score (TNSS). The mean baseline value was 8.5 in both groups. Error bars represent SD.

beginning with day 2 (except day 4) ( $P = .06$ ) (Table 3). For TNNSS, mean reductions from baseline were  $-1.8$  (mean change, 30.6%) and  $-1.5$  (mean change, 25.9%) with desloratadine and placebo, respectively ( $P < .001$ ) (Fig 3). Desloratadine was significantly more effective than placebo in reducing TNNSS at all times and intervals ( $P \leq .01$ ). Improvement in nasal and nonnasal symptoms was observed beginning on day 2 (Table 3).

Finally, treatment with desloratadine resulted in significantly greater improvement (mean reduction from baseline,

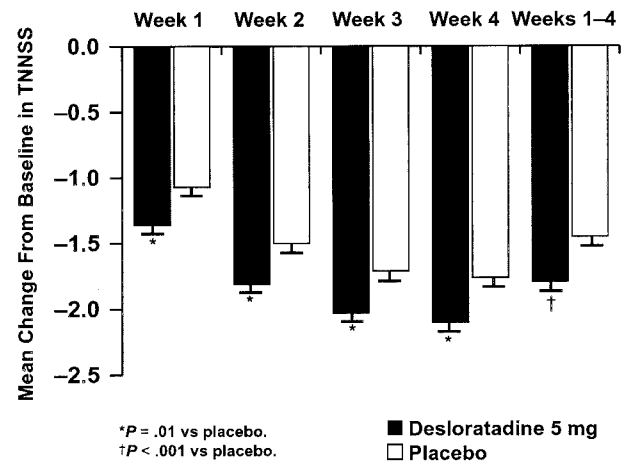


Figure 3. Mean change from baseline in total nonnasal symptom score (TNNSS). Mean baseline values were 5.8 and 5.7 for the desloratadine-treated and placebo groups, respectively. Error bars represent SD.

$-0.65$  [mean change, 24.2%]) in the overall condition of PAR compared with that observed in the placebo group (mean reduction from baseline,  $-0.53$  [mean change, 19.5%];  $P = .01$ ). Both treatment groups demonstrated an increase in PNIF during the study; however, the increases for each interval were consistently greater in patients receiving desloratadine. The mean increase from baseline in morning PNIF was significantly greater in the desloratadine group than in the placebo group: 10.2 L/min vs 7.6 L/min ( $P = .03$ ) (Fig 4). Evening PNIF values increased by 11.2 L/min and 8.9 L/min with desloratadine and placebo, respectively; however, the difference only approached significance ( $P = .07$ ).

Desloratadine was safe and well tolerated, with an adverse event profile similar to that observed with placebo use (Table 4). Overall, adverse events were reported in 34% and 33% of patients treated with desloratadine and placebo, respectively.

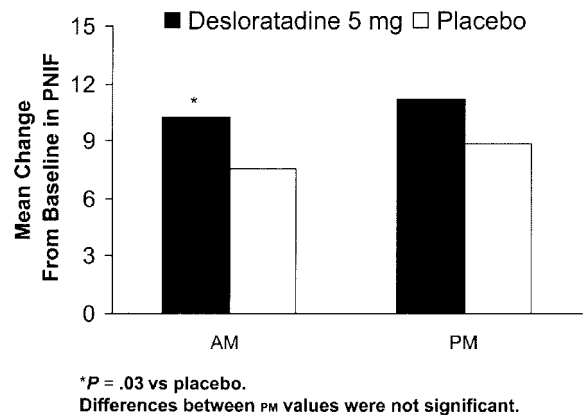


Figure 4. Overall mean change from baseline in morning (AM) and evening (PM) peak nasal inspiratory flow (PNIF) values. Morning/evening baseline values were 92.2/96.0 and 93.9/97.3 for the desloratadine-treated and placebo groups, respectively.

Table 4. Treatment-Emergent Adverse Events Occurring in at Least 2% of the Patients

Adverse event	Patients, No. (%)	
	Desloratadine, 5 mg, group (n = 591)	Placebo group (n = 588)
Headache	33 (6)	36 (6)
Upper respiratory tract infection	35 (6)	26 (4)
Pharyngitis	16 (3)	16 (3)
Nausea	9 (2)	12 (2)
Coughing	7 (1)	12 (2)

The most frequently reported treatment-emergent adverse events were headache (reported in 6% of patients in both groups) and upper respiratory tract infection (reported in 6% of patients in the desloratadine group and 4% in the placebo group). Adverse events led to study discontinuation in 5% of patients receiving desloratadine compared with 3% of those receiving placebo. No serious or unexpected adverse events were attributed to desloratadine therapy, and no deaths occurred during the study. No clinically relevant changes in mean vital signs or ECG intervals (including QT<sub>c</sub>) were observed. Heart and rhythm disorders were reported in 1 patient (0.2%) receiving desloratadine and in 3 (0.5%) receiving placebo.

## DISCUSSION

Although antihistamines are commonly prescribed for PAR, only a few published studies have detailed their effects in the treatment of PAR. This study demonstrates that desloratadine, 5 mg once daily, provides significantly greater symptom relief compared with placebo in patients with PAR, thus confirming the findings of a previous study by Simons and colleagues.<sup>15</sup>

Simons et al<sup>15</sup> evaluated the effects of desloratadine, 5 mg once daily, in a 4-week, double-blind, placebo-controlled study involving 634 patients with PAR. The study demonstrated that desloratadine therapy significantly improved TSSs, TNSSs, and TNNSSs compared with placebo use; however, it did not include any objective measures of treatment response, such as PNIF. In contrast, the present study demonstrates that desloratadine therapy provides statistically significant improvement in subjective and objective measures of symptom control. Desloratadine therapy was associated with statistically significantly greater reductions from baseline in mean morning/evening reflective TSSs for each week of the study and during the entire study (primary end point) and in the mean change from baseline in TNSSs and TNNSSs. Objective improvement with desloratadine use was demonstrated by a statistically significant increase in morning PNIF and an increase in evening PNIF that approached statistical significance.

Onset of symptom relief in the present study was rapid (ie, improvement was evident by day 2 of the study), and efficacy

was maintained throughout the 24-hour dosing interval and for the duration of the study. The statistically significant improvements in the secondary efficacy end points of TNSS and TNNSS demonstrate that desloratadine is effective for the nasal and nonnasal components of PAR. Furthermore, in a separate study<sup>10</sup> of desloratadine in SAR, a pattern of effect similar to that observed in the present study was seen, with the reduction from baseline in TSS (TNSS and TNNSS) occurring between days 1 and 3, continuing to day 4, and leveling off until day 7 (but remaining statistically significantly different from placebo). However, symptom scores continued to decrease from baseline between week 1 and week 2, and the apparent lack of effect during the second half of the first week observed in both studies does not seem to affect the longer-term efficacy of desloratadine. Also consistent with the results of earlier studies<sup>10,11,13</sup> in patients with SAR or PAR, desloratadine was safe and well tolerated, with an adverse event profile similar to that of placebo.

In patients with AR, measurement of PNIF provides an objective evaluation of the obstruction of nasal airflow, which enables accurate evaluation of the patient's condition. It provides a more objective index of treatment response than subjective symptom scores because nasal airflow obstruction represents an important component of the perennial allergic process.<sup>16</sup> In this study, patients who received desloratadine demonstrated a statistically significantly greater improvement in mean morning PNIF than those receiving placebo.

In conclusion, although the efficacy and safety of H<sub>1</sub>-antihistamines in the treatment of SAR have been well documented, data regarding their use in patients with PAR are, in comparison, somewhat limited. Collectively, the results of this study, which confirm and extend the findings of a previous PAR study, demonstrate that desloratadine is safe and is associated with statistically significant reductions in the nasal and nonnasal symptoms associated with PAR. In addition, this study found that objective morning PNIF values are statistically significantly improved by the administration of desloratadine.

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