

Desloratadine for the treatment of cypress pollen-induced allergic rhinitis

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Background: Few studies have been conducted to assess treatment options for patients with sensitivities to cypress pollens, important triggers of allergic rhinitis (AR) in the Mediterranean region.

Objective: To evaluate the effect of desloratadine, a second-generation antihistamine, on AR symptoms caused by cypress pollens native to France.

Methods: Adults (N=233) with symptomatic cypress pollen allergies were randomized to receive desloratadine, 5 mg, or placebo daily for 15 days during 2 consecutive cypress pollen seasons. The primary end point was the percentage change from baseline in morning total nasal symptom scores on day 14; secondary assessments included total symptom score, peak nasal inspiratory flow, the Rhinoconjunctivitis Quality of Life Questionnaire, and global response to therapy.

Results: On day 14, the desloratadine group had a significantly greater percentage decrease in total nasal symptom score vs the placebo group (−40% vs −30%; $P < .04$). Similarly, on day 14, there was a 47% and 37% respective decrease in total symptom score ($P = .01$). Mean peak nasal inspiratory flow scores showed numeric, albeit not statistically significant, improvements from baseline through day 14 with desloratadine. A significantly greater improvement in Rhinoconjunctivitis Quality of Life Questionnaire scores occurred with desloratadine vs placebo on day 14 (−1.4 vs −0.9; $P = .004$). The mean global response to therapy was better with desloratadine vs placebo (3.4 vs 3.9; $P = .004$). The adverse event rate was similar in both groups.

Conclusion: Desloratadine is efficacious and safe for the treatment of AR induced by cypress pollens; it also improved disease-related quality of life.

Ann Allergy Asthma Immunol. 2009;103:260–266.

INTRODUCTION

Several varieties of cypress trees are found in the countries surrounding the Mediterranean Sea, the most common being *Cupressus sempervirens*, *Cupressus arizonica*, and *Cupressus lusitanica*.¹ *Cupressus arizonica*, the most thoroughly characterized,¹ has 6 IgE-binding protein bands; the 43-kDa component has the greatest intensity and highest frequency of recognition by human IgE.^{1,2} Extracts of *C arizonica* have greater allergenic potential than those of other cypress varieties.³ A study exploring the biological activities of *C arizonica* pollen showed that it retains allergenic potency up to 6 years after collection.

Patients sensitized to cedar pollen often experience the clinical symptoms of allergic rhinitis (AR) outside the pollen season.⁴ AR has traditionally been classified as seasonal (SAR) or perennial (PAR) based on time and type of allergen exposure. The Allergic Rhinitis and its Impact on Asthma working group has reclassified AR as intermittent (IAR) (ie, symptoms present for <4 days per week or <4 consecutive weeks) or persistent (PER) (symptoms present for >4 days per week and >4 con-

secutive weeks), depending on symptom severity and duration, and mild or moderate/severe according to its impact on quality of life (QoL).⁵ Although SAR and PAR are not interchangeable with IAR and PER, respectively,⁵ 2 cross-sectional surveys conducted in France in patients with SAR (N = 3026) and PAR (N = 3507) found that 43.7% of those diagnosed as having SAR also fulfilled the criteria for PER and that 44.6% of those diagnosed as having PAR met the requirements for IAR.⁶

In the Mediterranean region, cypress pollen allergy has become increasingly common since the late 1980s and is now the leading cause of SAR.^{7–9} The cypress tree is the most plentiful plant in this region,¹⁰ proliferating in recent decades because of landscaping, reforestation, and wind/noise barriers.^{11,12} Consequently, the annual total concentration of airborne cypress pollen has increased in many areas.^{13,14}

During the past few years, cypress pollen sensitization rates have grown substantially, with significantly higher rates of positive skin test results and SAR symptoms found in areas where residents have greater levels of exposure.^{8,12,15} Further, because of a high degree of sequence homology,¹⁶ patients sensitized to cypress pollen may cross-react to other conifer pollens such as mountain cedar.¹⁷ Cypress pollen AR manifests with severe nasal symptoms that may be accompanied by conjunctivitis, dry cough, and asthma.^{12,15} Symptoms appear most often during the winter and early spring, when peak pollination typically occurs.^{1,12,15,18}

The growing prevalence of cypress pollen AR and the debilitating nature of the symptoms have prompted efforts to evaluate

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Disclosures: Drs Dreyfus and Mesbah are employees of Schering-Plough France.

Funding Sources: This study was supported by Schering-Plough.

Trial Registration: clinical trials.gov Identifier: NCT00867191.

Received for publication January 26, 2009; Received in revised form March 4, 2009; Accepted for publication April 1, 2009.

the effectiveness of available treatment options. This study evaluated the effectiveness of desloratadine, a second-generation antihistamine with proven efficacy in treating SAR, in relieving symptoms among patients with symptomatic cypress pollen allergies.

METHODS

This double-blind, placebo-controlled, randomized, parallel-group study was conducted at 34 centers in France in 2002 and 2003 during consecutive cypress pollen seasons. This study was performed in accordance with the Declaration of Helsinki, the guidelines of Good Clinical Practice, and French laws and regulations. The protocol was reviewed by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale and the independent ethics committees at each center. Patients signed an informed consent form before enrollment.

Inclusion/Exclusion Criteria

Patients were considered eligible if they were 18 years or older, had a 2-year history or longer of AR during the natural French cypress pollen season (from January to March), were clinically symptomatic with cypress pollen AR at baseline (total nasal symptom score [TNSS] plus total nonnasal symptom score [TNNSS] ≥ 8 [of a possible 18] with a nasal congestion score ≥ 2 [of a possible 3]), and had a positive skin prick test result (allergen papule diameter ≥ 3 mm) to cypress pollen and/or a positive cypress pollen specific IgE radioallergosorbent test result obtained within 24 months of the initial screening visit (or at the screening visit, if one had not been previously obtained). Women of childbearing potential were allowed to participate if they were using a medically acceptable birth control method and had a negative urine pregnancy test result at baseline. Patients were excluded if they had rhinitis medicamentosa, an upper respiratory tract or sinus infection requiring antibiotic therapy within 14 days before the screening visit, a viral upper respiratory tract infection within 7 days before baseline, nasal structural abnormalities significantly interfering with nasal airflow, or current evidence of any clinically significant disease or disorder that might interfere with study evaluations or affect patient safety.

Patients taking prohibited medications (eg, corticosteroids, cromolyn, antihistamines, or leukotriene inhibitors) or receiving immunotherapy to cypress pollen were enrolled after an appropriate washout period (Table 1). For patients not taking prohibited medications, the first visit was combined with the second (baseline).

Randomization and Assessments

Eligible patients were randomized to receive desloratadine, 5 mg/d, or placebo in the morning for 15 days. At baseline (day 0 to the first day of dosing) and on days 1, 3, and 14, investigators and patients evaluated the severity of TNSS (ie, rhinorrhea, congestion, sneezing, and itching) and TNNSS (ie, ocular itching, tearing, and redness and itchy ears/palate) during the previous 12 hours, using a 4-point scale (from 0 [no sign or symptom evident] to 3 [severe symptoms]). Peak nasal inspiratory flow (PNIF) was measured 3 times at each

Table 1. Washout Periods for Prohibited Medications

Medications prohibited during the trial	Washout period
Antihistamines	
Long-acting prescription agents (eg, cetirizine, fexofenadine, and loratadine)	5 d
Short-acting agents (eg, chlorpheniramine and hydroxyzine)	3 d
Topical nasal or ocular agents (eg, azelastine and levocabastine)	5 d
Corticosteroids	
High-potency dermatological agents	7 d
Intramuscular or intra-articular agents	30 d
Oral, inhaled, intravenous, rectal, intranasal, or ocular agents	7 d
Decongestants	
Local	1 d
Oral	3 d
Immunotherapy to cypress pollen	1 y
Investigational antibodies for asthma or allergic rhinitis	90 d
Investigational medications	30 d
Leukotriene inhibitors (eg, montelukast)	7 d
Mast cell stabilizers (eg, cromolyn, lodoxamide, and nedocromil), given by the intranasal, ocular, inhaled, or oral route	2 d

visit, with the best of the readings recorded. Patients evaluated symptoms every morning and evening and recorded the results in diaries, along with twice-daily PNIF values. The validated French-language version of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was completed by each patient at baseline and on day 14. The RQLQ uses a 7-point scale (from 0 [no impairment] to 6 [severe impairment]) to evaluate 7 domains: sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, activities, and emotions.¹⁹ On day 14, the investigator evaluated the global response to therapy using a 5-point scale (from 1 [complete relief] to 5 [no relief]). Adverse events (AEs) were evaluated at each visit.

Primary and Secondary End Points

The primary efficacy end point was the percentage change in the morning TNSS from baseline to day 14. Secondary end points included area under the curve (AUC) for the percentage change in TNSS, total symptom score (TSS) (TNSS plus TNNSS), and PNIF from baseline to days 3 and 14. Changes in RQLQ scores from baseline to day 14 and investigator assessments of global response to therapy were also measured.

Statistical Analysis

Demographic and baseline data were compared in both treatment groups using the χ^2 or Fisher exact test for nominal data, the Mann-Whitney test for ordinal data (symptom scores), and the *t* test for quantitative data. The principal efficacy analysis was based on the intent-to-treat (ITT) population (all patients who received ≥ 1 dose of study treatment and had ≥ 1 evaluation on day 1 of the primary end point). The Mann-

Whitney test was used to compare desloratadine with placebo for primary and secondary end points. The global therapeutic response analysis was analyzed by the χ^2 and Mann-Whitney tests. The safety analysis was based on data collected from patients who received study treatment at least once. All statistical tests were 2-tailed at the .05 level of significance.

RESULTS

Demographics

Of the 236 patients screened, 233 were randomized (118 to desloratadine and 115 to placebo). Three patients were excluded because of insufficient symptom severity scores or unavailable treatment information. Nine randomized patients were excluded from the efficacy analysis because of protocol deviations. Therefore, the ITT analysis was based on data from 224 patients: 113 in the desloratadine group and 111 in the placebo group. Forty-six patients given desloratadine and 54 given placebo withdrew from the study prematurely. The reasons for early withdrawal were treatment failure (34 in the desloratadine group and 44 in the placebo group), AEs (3 in the desloratadine group and 5 in the placebo group), consent withdrawal (6 in the desloratadine group and 2 in the placebo group), or other (3 in the desloratadine group and 3 in the placebo group).

The baseline characteristics of all randomized patients are given in Table 2. The percentage of women was higher in the placebo group than in the desloratadine group ($P = .04$). There were no significant differences between the populations for any other parameters at baseline.

Efficacy

Nasal and nonnasal symptoms. In the ITT population, the percentage change in the morning TNSS from baseline to day 14 was significantly greater in the desloratadine group than in the placebo group (-40% vs -30% ; $P < .04$) (Fig 1). The AUC for the percentage change in TNSS was consistent with the analysis of the primary end point, with significant im-

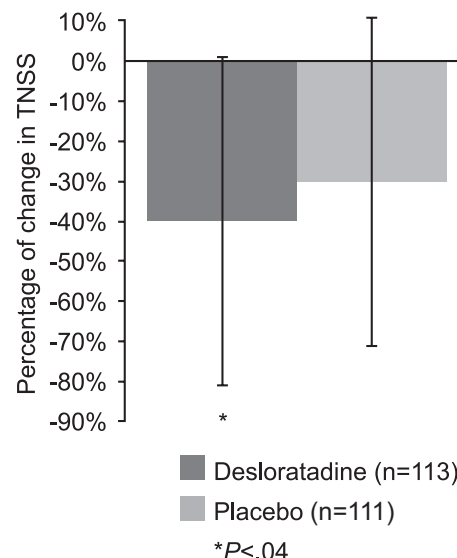


Figure 1. Percentage change from baseline to day 14 in total nasal symptom score (TNSS) in the intent-to-treat population. Bars equal SD.

provements seen with desloratadine compared with placebo from day 0 to day 3 (-0.87 vs -0.69 ; $P = .03$) and from day 0 to day 14 (-5.16 vs -3.93 ; $P = .04$). On day 1, the mean improvement in TNSS was -3.5 with desloratadine and -2.9 with placebo ($P = .08$).

Marked relief in TSS was also observed. The AUCs for the percentage change in TSS showed significantly greater improvement in patients taking desloratadine, compared with those taking placebo, from day 0 to day 14 (-0.88 vs -0.66 ; $P = .02$). Both patient populations had a moderate mean symptom score severity (TSS ≥ 8 and nasal congestion and nonnasal symptom score ≥ 2) at baseline. On day 1, individual symptom severity improved to mild (mean individual symptom score of 1.4) in the desloratadine population but remained moderate in the placebo population (mean individual symptom score of 1.8), whereas TSS decreased by 40% in the desloratadine group and by 26% in the placebo group (Fig 2). A decreased rate of individual symptom severity was seen on day 3 (mean score of 1.1 with desloratadine and 1.4 with placebo; TSS decreased by 54% and 41%, respectively; $P = .01$). On day 14, the mean individual symptom score was 1.2 with desloratadine and 1.6 with placebo; there was a 47% and 37% respective decrease in TSS ($P = .01$).

The mean percentage change from baseline to day 14 in individual nasal symptom scores of sneezing and itching was significantly greater for desloratadine vs placebo (-0.59 vs -0.44 [$P = .02$] for sneezing and -0.48 vs -0.29 [$P = .04$] for itching) (Fig 3). The percentage change values in the individual symptoms of rhinorrhea and nasal congestion with desloratadine vs placebo were -0.40 vs -0.35 ($P = .58$) and -0.33 vs -0.27 ($P = .35$), respectively.

Other assessments. On day 14, the mean overall decrease from baseline in RQLQ scores (indicating improvement) was significantly greater with desloratadine vs placebo (-1.4 vs

Table 2. Study Population Baseline Characteristics^a

Characteristics	Desloratadine group (n = 118)	Placebo group (n = 115)
Age, y	40.3 (13.8)	39.2 (12.4)
Female sex, No. (%)	60 (50.8)	71 (61.7)
Symptom scores ^b		
Congestion	2.4 (0.5)	2.4 (0.6)
Rhinorrhea	2.1 (0.8)	2.2 (0.8)
Sneezing	2.1 (0.8)	2.1 (0.9)
Nasal itching	1.7 (1.0)	1.8 (0.9)
Ocular symptoms	2.2 (0.8)	2.2 (0.8)
Ear or palate itching	1.4 (1.0)	1.6 (0.9)
TNSS	8.6 (1.7)	8.9 (1.9)
RQLQ scores	3.3 (0.9)	3.3 (1.1)

Abbreviations: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, total nasal symptom score.

^a Data are given as mean (SD) unless otherwise indicated.

^b Investigators' evaluations.

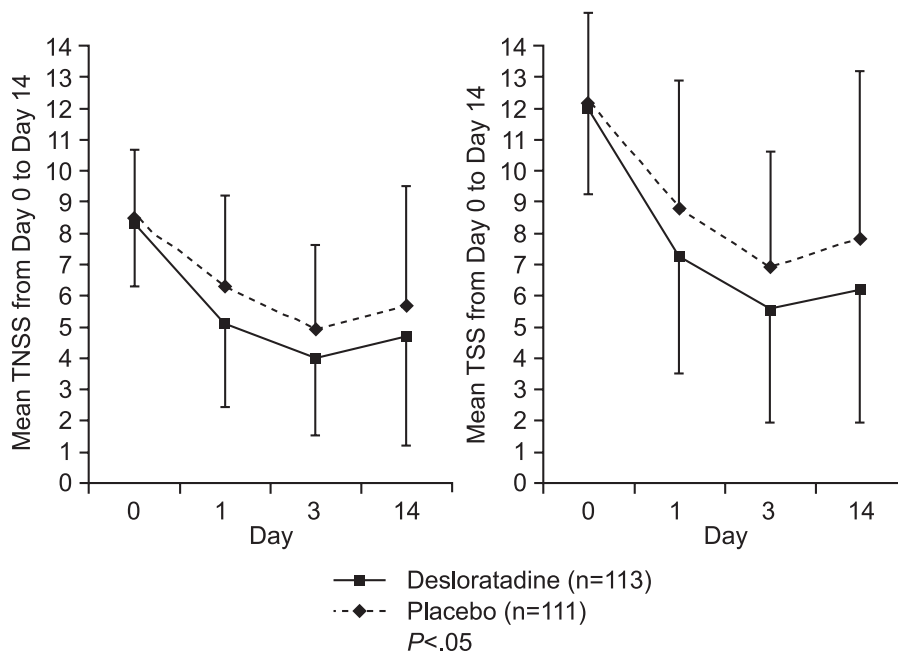


Figure 2. Total nasal symptom score (TNSS) (A) and total symptom score (TSS) (B): area under the curve of the percentage change from day 0 to day 3 and to day 14 in the intent-to-treat population. Bars equal SD.

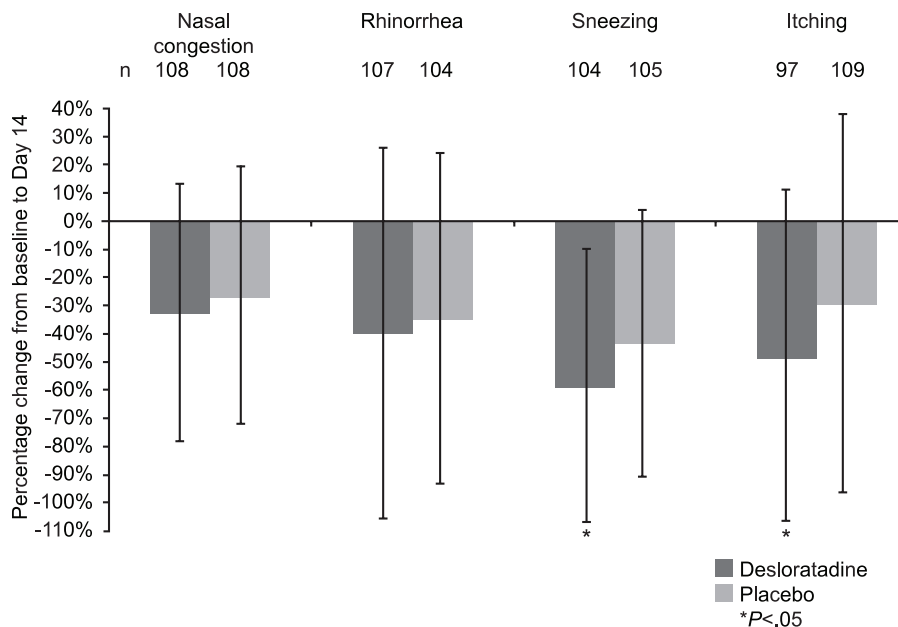


Figure 3. Percentage change from baseline to day 14 in individual nasal symptom scores. Bars equal SD.

−0.9; $P = .004$) (Fig 4). All individual RQLQ domain scores except sleep significantly improved in patients given desloratadine compared with placebo: non-nose/eye symptoms (−1.0 vs −0.6; $P = .009$), practical problems (−2.1 vs −1.2; $P < .001$), nasal symptoms (−1.8 vs −1.3; $P = .01$), eye symptoms (−1.4 vs −0.9; $P = .01$), emotions (−0.9 vs −0.6; $P = .03$), and

activities (−1.5 vs −1.0; $P = .02$). Scores for the sleep domain were numerically better with desloratadine vs placebo (−1.1 vs −0.8; $P = .13$).

After treatment, PNIF scores improved from baseline through day 14 in both groups. The improvement was more notable with desloratadine than with placebo (26% vs 20%) on day 1, al-

though this difference did not reach statistical significance. No statistically significant differences were found between the desloratadine and placebo groups for AUC of the percentage change for day 0 to day 3 or to day 14, although mean values with desloratadine vs placebo were higher (−19.4 vs −11.2 for days 0 to 3 and −154.7 vs −104.1 for days 0 to 14).

An investigator evaluation of global response to therapy was performed on day 14. The mean score was significantly more favorable for desloratadine compared with placebo (3.4 vs 3.9; $P = .004$).

Safety

The most frequent AE noted for all patients was headache, often caused by sinusitis (Table 3). AEs that were considered to be probably or possibly related to treatment occurred in 9.3% and 7.0% of patients in the desloratadine and placebo groups, respectively. Most AEs were mild to moderate; 3 AEs, all in those given placebo, were severe. Fewer patients taking desloratadine (2.5%) withdrew because of AEs than those taking placebo (4.3%).

DISCUSSION

Numerous randomized, placebo-controlled trials have been conducted outside France in patients with SAR caused by grass and ragweed pollen; these patients were treated with once-daily desloratadine, 5 mg. The present study was designed to obtain similar data specific to the Mediterranean region of France, where cypress pollens have become the major cause of SAR.⁸ All indications point toward continuing increasing exposure and sensitization to these pollens due to the widespread planting of cypress trees.¹¹ Cypress pollen-related AR may also be associated with more severe symptoms than other forms of SAR.¹ These observations underscore the need for a greater understanding of the efficacy of various available treatments for the relief of cypress pollen-related AR symptoms.

Second-generation antihistamines, recommended by the Allergic Rhinitis and its Impact on Asthma working group for all

forms of AR,⁵ have been infrequently studied in the setting of cypress pollen allergy.²⁰ In a 4-week study of 27 patients with SAR due to cypress or *Parietaria*, randomized to receive astemizole or terfenadine, both treatments were associated with significant reductions in AR symptoms, with no between-group differences.²⁰ Notably, 7 patients (26%) withdrew from the study after 1 week because of lack of symptom relief. The investigators speculated that the dropout rate may have been because 6 of the 7 patients were sensitized to cypress pollen rather than *Parietaria* pollen.²⁰ Other studies have explored the use of second-generation antihistamines for the treatment of allergy to mountain cedar pollen, which comes from a closely related allergenic species, *Juniperus ashei*.⁸ In a 14-day randomized study of 676 patients with mountain cedar pollen allergy, the combination of the second-generation antihistamine acrivastine plus pseudoephedrine was significantly more effective than either agent alone or placebo for relieving AR symptoms ($P < .001$).²¹

In this study, desloratadine treatment was significantly more effective than placebo in relieving nasal symptoms associated with cypress pollen-related AR, shown by the percentage change from baseline in TNSS and TSS. An analysis of the AUC for TNSS and TSS supported the results of the primary analysis. Nasal and nonnasal symptoms were reduced with desloratadine treatment from moderate to mild intensity, as early as day 1 and continuing through day 14. These findings are consistent with results from earlier trials in patients with SAR and PAR. A 14-day trial of 219 patients with SAR found that the reduction in combined patient/investigator-rated TSS was significantly greater with desloratadine than placebo ($P = .03$).²² Similar significant results were observed for TNSS ($P = .02$). In a 4-week trial ($N = 676$) in patients with PAR, the mean change from baseline in morning/evening instantaneous and reflective TSS was significantly greater with desloratadine vs placebo ($P = .005$ and $P = .007$, respectively).²³ In the present study, the difference in TNSS score between desloratadine and placebo was 10%, not as robust as the results in these previous studies.^{22,23} This may be due in part to more rapid onset and severity of symptoms observed in patients with cypress pollen-related SAR.¹

In this study, PNIF scores also improved after desloratadine treatment on day 1, although the mean difference from placebo was not statistically significant. This may mirror the nonsignificant change in nasal congestion scores, although congestion in those with cypress pollen allergy is often severe. All patients in this study had a baseline congestion score of 2 or greater (scale, 0–3).

The results from this study diverge from those of other randomized, double-blind, placebo-controlled studies in patients with SAR and PAR that have found a significant effect on nasal congestion with desloratadine. In a meta-analysis of studies in patients with AR, desloratadine treatment reduced total and nasal symptoms of SAR and PAR and improved objective measures of nasal airflow.²⁴ Patients with a history of SAR in 2 crossover studies^{25,26} had significantly higher nasal airflow ($P =$

Table 3. Most Frequently Reported Adverse Events^a

Adverse events	Desloratadine group (n = 118)	Placebo group (n = 115)
Headache	9 (7.6)	11 (9.6)
Dry mouth	5 (4.2)	1 (0.9)
Coughing	3 (2.5)	1 (0.9)
Abdominal pain	2 (1.7)	0 (0)
Epistaxis	2 (1.7)	2 (1.7)
Gastroenteritis	2 (1.7)	3 (2.6)
Pruritus	2 (1.7)	0 (0)
Somnolence	2 (1.7)	2 (1.7)
Insomnia	1 (0.8)	2 (1.7)
Nausea	1 (0.8)	3 (2.6)
Rhinitis	1 (0.8)	2 (1.7)
Total reporting at least 1 adverse event	34 (28.8)	34 (29.6)

^a Data are given as number (percentage) of each group. Only events occurring in more than 1 subject in either treatment group are listed.

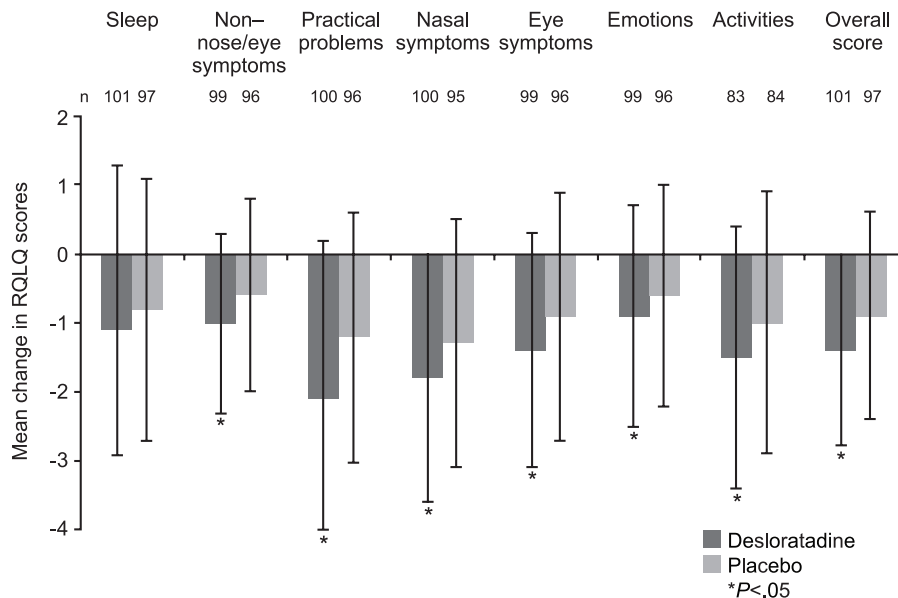


Figure 4. Mean change from baseline to day 14 in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores. Bars equal SD.

.006) and reduced individual congestion scores ($P \leq .001$ for both) with desloratadine vs placebo.

In another study, desloratadine treatment significantly ($P = .03$) increased morning PNIF compared with placebo ($P = .03$).²⁷ Evening PNIF values also increased with desloratadine, although not to the level of significance, and TSS (including congestion) was significantly lower with desloratadine than placebo by day 2 ($P = .001$).

Desloratadine therapy improved QoL in this study, as reflected by improvements in the RQLQ scores, even though a statistically significant improvement was not reached for every nasal symptom. Improvement in nasal symptoms does not correlate perfectly with QoL alterations.²⁸ Desloratadine has been shown to improve QoL in other studies of patients with AR. In 1 study, 483 patients with SAR who were randomized to receive desloratadine, 5 mg/d, or placebo for 14 days were evaluated for improvements in QoL as measured by the RQLQ. Significant decreases in total RQLQ scores ($P < .001$ vs placebo) and individual domain scores ($P \leq .04$ for all) were noted with desloratadine on day 14.²⁹ Another 14-day study of 218 patients with SAR given desloratadine, 5 mg/d, or placebo found significant improvements in the nasal symptom domain of the RQLQ with desloratadine vs placebo ($P = .03$).²²

Study results indicate that the improvements produced by desloratadine treatment are clinically relevant. The symptom severity in the patients receiving desloratadine decreased from moderate to mild, as evidenced by the significant improvement in morning TNSS, TSS, sneezing, and itching and the numeric improvement in rhinorrhea and nasal congestion. In patients receiving placebo, symptom severity decreased but remained moderate.

For RQLQ, the minimal important difference, or the smallest difference in an RQLQ domain that could be perceived as

beneficial,³⁰ has been shown to be approximately 0.57.³¹ Improvement with desloratadine treatment, noted for total RQLQ and all individual domains, exceeded the minimal important difference of 0.57. This effect was also observed in the placebo group. However, there was a 55% improvement in total RQLQ score with desloratadine treatment over placebo; improvement for desloratadine vs placebo in individual RQLQ domain scores ranged from 38% to 75%, including the sleep domain, which improved numerically with desloratadine treatment.

The rate of AEs was low with desloratadine treatment and comparable to that of placebo, with no unexpected or serious AEs occurring during the study. The substantial number of withdrawals from study medication due to treatment failure (28.8% in the desloratadine group and 38.2% in the placebo group) may have been because the study was conducted during an explosive period of cypress pollination, associated with extremely high levels of pollen exposure and greater severity of symptoms. Indeed, most symptoms were rated as moderate to severe at baseline.

Significantly more women were included in this study ($P = .04$); this difference was particularly remarkable in the placebo group, in which 61.7% of the group was female (vs 50.8% in the desloratadine group). However, this was unlikely to influence the response to treatment. In addition, cypress pollen counts were not monitored at every study location, primarily because the study was conducted during the cypress pollen season when counts were expected to be high. Furthermore, individual pollen exposure is difficult to ascertain; factors such as weather conditions, frequency and duration of outdoor activity, and individual sensitivity contribute to wide variations in pollen level and amount of exposure to pollens even within a geographic area.³²

Desloratadine treatment had an onset of action as early as day 1 and maintained its beneficial effects in patients with cypress

pollen AR during the 14-day study. These results are particularly noteworthy given that exposure to cypress pollen is becoming more widespread and severe and that the risk of sensitization in Mediterranean populations is increasing. The improvements in symptom relief and QoL observed with desloratadine and its low rate of AEs, similar to that of placebo, suggest that this agent is a safe, effective treatment option for this increasingly prevalent form of AR.

ACKNOWLEDGMENTS

Editorial assistance was provided by Patricia C. Abramo. This assistance was funded by Schering-Plough.

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