

ORIGINAL ARTICLE

Evaluation of desloratadine on conjunctival allergen challenge-induced ocular symptoms

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Summary

Background Allergic conjunctivitis (AC) is frequently associated with allergic rhinitis (AR) and affects up to 91% of patients with AR. Desloratadine, an orally administered, non-sedating second-generation antihistamine, has proven efficacy and safety in the control of nasal and non-nasal – including ocular – symptoms of AR. This randomized-controlled trial is the first to evaluate the effects of continuous oral desloratadine treatment on ocular symptoms after conjunctival allergen challenge.

Objective To evaluate the impact of administering oral desloratadine 5 mg daily for 7 days on ocular symptoms in conjunctival allergen-challenged subjects.

Methods In this crossover study, adults with a history of seasonal AC and a minimal threshold response to allergen challenge were randomized to receive desloratadine 5 mg daily ($n = 20$) or placebo ($n = 21$) for 7 days after which they underwent a second ocular allergen challenge. After a 2-week washout period, subjects crossed over to the other treatment. The primary efficacy parameter was the intra-subject difference from baseline at end-point in the post-challenge mean composite ocular redness score (the sum of redness scores in ciliary, conjunctival, or episcleral vessel beds). Secondary efficacy parameters included the intra-subject and inter-subject differences in individual symptom scores for ciliary, conjunctival, or episcleral redness; pruritus; chemosis; eyelid swelling; and tearing.

Results The mean composite ocular redness score was reduced at 10, 15, and 20 min post-challenge with desloratadine treatment compared with placebo, though these differences were not statistically significant ($P = \text{NS}$). Desloratadine was significantly more effective than placebo in preventing post-challenge ocular pruritus ($P < 0.001$). Significant improvements post-challenge were also seen in ciliary and episcleral redness, chemosis, eyelid swelling, and tearing ($P < 0.05$ vs. placebo for all comparisons). Desloratadine was well tolerated.

Conclusion Treatment with desloratadine 5 mg daily for 7 days reduced allergic ocular symptoms following allergen challenge.

Keywords allergic conjunctivitis, allergic rhinitis, conjunctival allergen challenge, desloratadine, ocular symptoms, rhinoconjunctivitis

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Introduction

Allergic conjunctivitis (AC) frequently accompanies allergic rhinitis (AR), occurring in up to 91% of patients with AR [1–3] and in up to 40% of paediatric AR patients [4]. A review of the Third National Health and Nutrition Examination Survey database found that symptoms of AC affected 40% of US adults during a 12-month period, and from May to August, ocular symptoms due to pollen were

more prevalent than nasal symptoms in pollinosis patients [5]. Further, approximately 70% of adults with AR considered their ocular symptoms to be at least as severe as their nasal symptoms [6]. In the landmark 2007 Allergies in America survey, more than half of respondents with AR stated that watering (51%) and red/itching eyes (53%) were moderately to extremely bothersome [7]. Patients have also reportedly experienced ocular allergic symptoms for more than half the days in a week (3.88 and 3.96

in two different groups), implicating the unmet need of ocular allergy relief and the negative impact ocular allergic symptoms can have on quality of life [2]. Although some patients may complain of isolated ocular allergic symptoms, AC more commonly occurs in the setting of AR [6]. Isolated allergen challenge in the nose or the eyes produces local allergic symptoms [8]. The AR and its Impact on Asthma (ARIA) guidelines note that oral antihistamines prescribed for AR improve accompanying conjunctivitis [8] and allergic nasal symptoms can be seen after an ocular allergen challenge [9].

The efficacy of medications on the signs and symptoms of ocular allergy can be evaluated with the conjunctival allergen challenge (CAC) model, validated in the United States, Europe, and Japan. The CAC model was developed by Ophthalmic Research Associates Inc. (North Andover, MA, USA) and has been used for > 15 years in numerous clinical trials of ophthalmic drugs, including olopatadine 0.1% [10] and 0.2% [11], epinastine 0.05% [12], and ketotifen fumarate 0.025% [13]. One study compared systemic loratadine tablets alone or in combination with olopatadine ophthalmic solution 0.1% for the treatment of ocular itching due to AC [14]. The addition of olopatadine 0.1% to loratadine significantly reduced ocular itching compared with loratadine alone ($P < 0.05$). Therefore, a topical ophthalmic agent can be a valuable addition to systemic therapy when treating ocular allergy [14].

In sensitized subjects, direct conjunctival exposure to allergen leads to mast cell degranulation and release of histamine and other proinflammatory vasoactive mediators, such as tryptase, prostaglandin D₂, leukotrienes, ILs, and eotaxin. These mediators, primarily histamine, are responsible for the acute-phase reactions, such as ocular pruritus, which begins, peaks, and resolves in the first few minutes; redness and chemosis, which peak after about 10 min; and eyelid swelling which peaks after 15 min.

Oral antihistamines attenuate ocular and nasal allergic responses primarily by blocking activity at the H₁-histamine receptor. First-generation antihistamines (e.g. chlor-

pheniramine, diphenhydramine, promethazine, and triprolidine) are associated with adverse events (AEs) such as somnolence and anticholinergic effects. They have been largely replaced as treatment of choice by newer second-generation medications, such as desloratadine, fexofenadine, and levocetirizine.

Desloratadine is an orally active, potent, highly selective non-sedating second-generation antihistamine with proven efficacy and safety in the treatment of AR (seasonal, perennial, intermittent, and persistent). Although clinical studies in AR may include ocular symptoms as a secondary outcome, usually reported as total symptom scores, there are limited data specific to AC [2, 15]. To date, there has been one controlled clinical investigation of the efficacy of desloratadine treatment on seasonal AC, in which desloratadine was compared with ketotifen fumarate ophthalmic solution or a combination of the two medications [16]. The present study is the first randomized-controlled clinical trial to evaluate the effects of continuous desloratadine on the CAC-induced ocular symptoms of AC.

Methods

Study design

This double-blind, randomized, placebo-controlled, cross-over study investigated the impact of 7 days of desloratadine 5 mg once daily or placebo on allergen-provoked symptoms of AC in adults with a ≥ 2 -year history of AC associated with seasonal AR.

At visit 1 (day 0; baseline), subjects with an ocular symptom severity erythema score ≤ 1 (0–3 scale) underwent allergen challenge with escalating allergen concentrations instilled in the eyes at 10-min intervals to establish minimum response threshold (Fig. 1). The sensitizing allergen was identified by positive skin-prick test or by history in those subjects who had undergone allergen challenge in other studies.

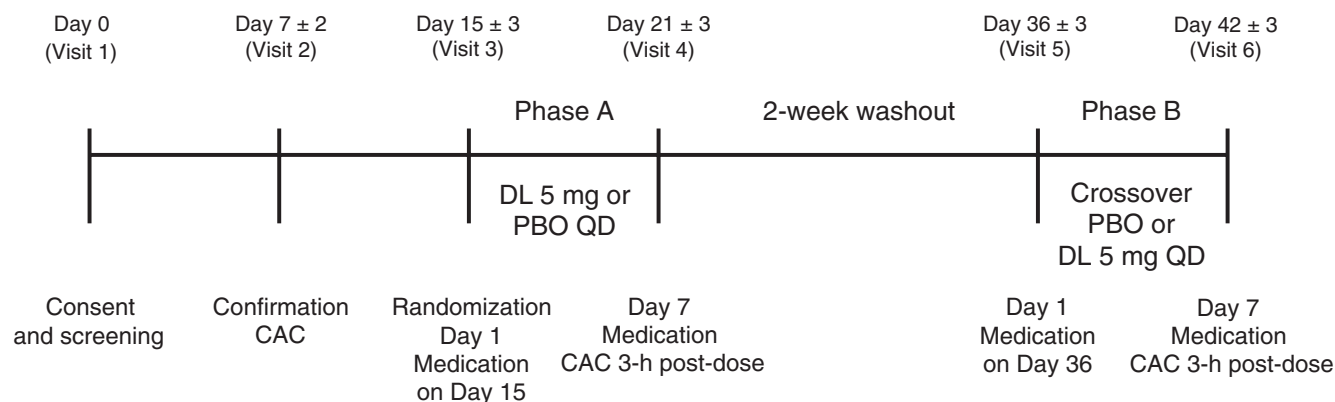


Fig. 1. Study design. DL, desloratadine; PBO, placebo; QD, once daily; CAC, conjunctival allergen challenge.

An initial qualifying response was defined as a bilateral ocular pruritus score ≥ 2 and a bilateral ocular redness score ≥ 2 within 10 min post-challenge. The allergen concentration that induced a qualifying response was recorded for each participant and used in all subsequent challenges. Multiple observers who had undergone redness-standardization training were used to control for potential variation in scoring.

At visit 2 (day 7), the second qualifying response to a confirmatory allergen challenge was established as a bilateral ocular pruritus score ≥ 2 and bilateral ocular redness score ≥ 2 . Subjects with a qualifying response to both challenges were randomized in a 1:1 ratio via computer-generated code to receive either desloratadine 5 mg once daily or placebo at visit 3 (day 15; phase A begins). At this visit, subjects received a dose of desloratadine or placebo and were instructed to continue once-daily dosing for 5 additional days. At visit 4 (day 21), subjects underwent another allergen challenge, and symptoms were evaluated at 3 h after receiving their final phase A study dose. Bilateral ocular redness, chemosis, eyelid swelling, and tearing were assessed at 10, 15, and 20 min post-challenge; bilateral ocular pruritus scores were analysed at 3, 5, and 7 min.

Phase B began on visit 5 (day 36). Subjects with a qualifying response to allergen challenge were crossed over to the alternate treatment after a 2-week washout period. Visits 5 and 6 (day 42) followed the same protocol as visits 3 and 4.

The study was conducted according to the Declaration of Helsinki and subsequent revisions and in compliance with Good Clinical Practice. The study protocol and consent forms were reviewed and approved by the Independent Ethics Committee or Institutional Review Board at each study centre. All subjects provided written informed consent.

Efficacy parameters

The primary efficacy parameter was the intra-subject difference in mean composite ocular redness score from baseline to post-challenge after treatment. Only subjects who had received at least one dose of desloratadine and had efficacy data from both phases were included. Severity scores for left and right eyes were combined.

Statistical analysis was performed on changes from baseline for each time-point using an ANOVA model for a 2×2 crossover design. Normality assumption of ANOVA was tested using the Shapiro-Wilk test.

The change from baseline for the secondary measures of individual ocular redness (ciliary, conjunctival, or episcleral vessel beds) and pruritus, chemosis, eyelid swelling, and tearing symptom scores were analysed using the method described above. An inter-subject analysis was conducted on scores for the same variables using phase A

data only. The two-sample *t* test was used to determine the difference in treatment effects between placebo and desloratadine on the change from baseline. This non-parametric analysis was performed as a confirmation of the parametric analysis results [17].

Safety analyses

Difference between treatments in overall AE incidence was evaluated using McNemar's test. Treatment-emergent AEs in phase A and the washout period were defined as new illness with onset on or after visit 3 or exacerbation of a pre-existing condition after start of the phase A treatment. Similarly, treatment-emergent AEs in phase B were described as new illness with onset on or after visit 5 or exacerbation of a preexisting (before phase A) condition after start of phase B treatment.

An increase of 0.22 or greater in ophthalmic examination and visual acuity was also considered an AE. Visual acuity assessment and slit-lamp examination were performed at baseline visit and pre- and post-challenge at visits 2, 3, 4, and 6.

Sample size estimate

The study was designed to enroll 36 subjects to detect a difference of 0.5 U in the composite ocular redness score with 90% power, assuming a standard deviation of 0.9. The between-subject analysis ($n = 18$ in each group) attained 90% power for differences over 1.0 U. To detect a 0.5-U difference in assessment scores between desloratadine and placebo groups, the power was 38%, assuming a common 0.9 U standard deviation.

Results

Seventy-six subjects were screened, and 41 subjects (63.4% women) with a confirmed qualifying allergen challenge response were randomized: 21 to the placebo-desloratadine treatment sequence and 20 to the desloratadine-placebo treatment sequence. Baseline demographics and clinical characteristics were not statistically different between subject groups (Table 1). Subjects were aged ≥ 18 years and reported AC usually (46%) or always (54%) associated with seasonal AR. Additional inclusion/exclusion criteria are listed in Table 2.

Primary efficacy result

The change from baseline in mean composite ocular redness scores at 10, 15, and 20 min post-challenge was lower with desloratadine treatment compared with placebo: 5.18, 5.43, and 5.30 vs. 5.84, 6.06, and 5.89, at 10, 15, and 20 min, respectively (Table 3). However, the

Table 1. Baseline demographics and clinical characteristics

	PBO-DL (n = 21)	DL-PBO (n = 20)	P
Gender			
Female, n (%)	11 (52.4)	15 (75)	0.138
Mean age, years (SD) (range, years)	39.1 (12.95) (18.6–70.6)	39.5 (11.31) (21.7–62.2)	0.927
Race/ethnicity, n (%)			0.590
White	20 (95.2)	18 (90.0)	–
Native Hawaiian/ Other Pacific Islander	0 (0)	1 (5.0)	–
Multiracial	1 (4.8)	1 (5.0)	–
Concomitant medications*, n (%)			
Analgesics	11 (52)	18 (90)	–
Antidiabetic agents	2 (10)	2 (10)	–
Antihistamines/decongestants	2 (10)	1 (5)	–
Cardiovascular agents	9 (43)	4 (20)	–
Gastrointestinal agents	2 (10)	2 (10)	–
Hormones	4 (19)	5 (25)	–
Nutritionals	2 (20)	11 (55)	–
Psychotherapeutic agents	3 (14)	3 (15)	–
Other	0 (0)	4 (20)	–
Mean baseline symptom scores (SE)			
Composite ocular redness	0.38 (0.11)	0.53 (0.11)	0.318
Ciliary redness score	0.09 (0.04)	0.14 (0.04)	0.406
Conjunctival redness score	0.21 (0.04)	0.24 (0.04)	0.623
Episcleral redness	0.08 (0.03)	0.16 (0.03)	0.127
Chemosis	0.01 (0.03)	0.08 (0.03)	0.066
Eyelid swelling	0.03 (0.02)	0.06 (0.02)	0.284
Itching	0 (0)	0 (0)	–
Tearing	0 (0)	0 (0)	–

*Over-the-counter antihistamine/vasoconstrictor combination ophthalmic solution could be instilled in the eyes of subjects who requested it following the last ocular allergic assessment at each of the challenge visits. Subjects were not allowed to use these relief drops at any other time during the study.
PBO, placebo; DL, desloratadine.

differences approached but did not reach statistical significance ($P = 0.07$, 0.08 , and 0.09 , respectively).

Secondary efficacy results

For the secondary intra-subject analyses, desloratadine treatment was significantly more effective than placebo at all post-challenge time-points in preventing ocular pruritus, chemosis, eyelid swelling, and tearing. At 3, 5, and 7 min post-challenge, the mean change from baseline in pruritus scores for desloratadine (1.45, 1.66, and 1.41, respectively) was significantly less ($P < 0.001$ for all comparisons) than those for placebo (2.24, 2.44, and 2.31, respectively) (Fig. 2). Similarly, the mean change in chemosis scores for desloratadine at 10, 15, and 20 min post-challenge was significantly less ($P = 0.020$, $P = 0.026$,

and $P = 0.003$, respectively) than placebo: 0.68, 0.71, and 0.67 vs. 0.93, 0.96, and 0.98, respectively (Fig. 3).

For eyelid swelling, mean change from baseline in score for desloratadine at all time-points (0.31, 0.42, and 0.39, respectively) was significantly less ($P = 0.002$, $P = 0.026$, and $P = 0.004$, respectively) compared with placebo (0.80, 0.76, and 0.86, respectively) (Fig. 4). In addition, mean change from baseline in tearing scores was significantly less for desloratadine than for placebo at all time-points ($P = 0.003$, $P < 0.001$, and $P = 0.001$, respectively) (Fig. 5). Mean scores for desloratadine were 0.37, 0.47, and 0.43, respectively, compared with placebo (0.79, 0.98, and 0.93, respectively).

Desloratadine reduced ciliary and episcleral redness at all time-points (10, 15, and 20 min); however, these differences were statistically significant at only the 10-min assessment. For ciliary redness, mean changes from baseline for desloratadine were 1.68, 1.78, and 1.74 compared with 1.94, 1.98, and 1.94 for respectively placebo ($P = 0.048$, 0.096 , and 0.116 , respectively). Similar results were found in episcleral redness score. Mean change from baseline at 10 min post-challenge for desloratadine (1.81) was significantly less ($P = 0.045$) than that for placebo (2.06). Nonetheless, at 15 and 20 min post-challenge, differences in mean change were not significant ($P = 0.064$ and 0.061 , respectively). There were no significant differences in mean change from baseline in conjunctival redness score at any time-point ($P = 0.218$, 0.150 , and 0.213).

The inter-subject analysis included phase A data only. Baseline pruritus scores equaled 0 for both treatments. Mean change from baseline at all time-points post-challenge in inter-subject pruritus for desloratadine (1.45, 1.64, 1.30) was significantly less than placebo (2.24, 2.51, 2.26) ($P < 0.03$). Both groups had the same baseline score (0) for tearing. Mean change in intra-subject tearing was also significantly less at 15 and 20 min post-challenge with desloratadine (0.55 and 0.42, respectively) than for placebo (1.12 and 1.05, respectively) ($P < 0.04$ and $P = 0.01$, respectively).

Safety

Subjects receiving desloratadine reported six (14.6%) treatment-emergent AEs compared with four (10.5%) in the placebo group. There were two (4.9%) treatment-related AEs in the desloratadine group compared with two (5.3%) in the placebo group. The most commonly reported treatment-related AE with desloratadine was dyspepsia (4.9%); in the placebo group, the most common treatment-related AEs were dry mouth (2.6%), pain in jaw (2.6%), dry throat (2.6%), and nasal dryness (2.6%). All AEs were mild or moderate; no subject discontinued because of an AE.

Table 2. Inclusion and exclusion criteria

Inclusion criteria

- Age ≥ 18 years
- At screening, women of childbearing potential must be using an acceptable birth control method and must have tested negative for pregnancy
- General good health
- ≥ 2 -year history of seasonal AC associated with seasonal AR
- Positive skin-prick test for grass, tree, cat dander, or ragweed allergens at screening or within 12 months before screening visit
- Calculated best-corrected bilateral visual acuity of ≥ 0.6 logMar as measured by ETDRS chart

Exclusion criteria

- Pregnant or nursing women
- Abnormal physical examination
 - Significant disease, particularly those that interfere with absorption, distribution, metabolism, or excretion of the study drug
 - Respiratory or ocular infection during the 4 weeks before screening
 - History of asthma
 - Upper respiratory tract or sinus infection requiring antibiotic therapy with last dose within 28 days before screening
 - Viral URI within 7 days before screening
 - Persistent symptoms of viral URI at the time of screening
 - Known upper gastrointestinal narrowing or abnormal esophageal peristalsis
- Treatment with inhaled or oral corticosteroids, β -2-agonists, cromones, theophylline, or leukotriene inhibitors who could not go through the washout periods and the entire study without using these medications
- History of intranasal drug abuse
- Known hypersensitivity, allergy, or idiosyncratic reaction to the study drug or its excipients
- Use of the study drug within 30 days before enrollment
- Immunotherapy within 24 h before any visit
- Unwilling to discontinue use of contact lenses during study
- Dependence upon nasal, oral, or ocular decongestants; nasal topical antihistamines; or nasal steroids

AC, allergic conjunctivitis; AR, allergic rhinitis; ETDRS, Early Treatment Diabetic Retinopathy Study; URI, upper respiratory infection.

Table 3. Change in mean composite ocular redness score*

	DL (<i>n</i> = 37)	PBO (<i>n</i> = 37)	<i>P</i> value [†]	95% CI
10 min post-challenge				
Mean (SD)	5.72 (2.12)	6.20 (1.96)	–	–
Mean change (SE)	5.18 (0.25)	5.84 (0.25)	0.066	–1.38, 0.05
15 min post-challenge				
Mean (SD)	6.01 (2.01)	6.42 (1.94)	–	–
Mean change (SE)	5.43 (0.24)	6.06 (0.24)	0.076	–1.32, 0.07
20 min post-challenge				
Mean (SD)	5.86 (2.00)	6.26 (2.00)	–	–
Mean change (SE)	5.30 (0.24)	5.89 (0.24)	0.086	–1.27, 0.09

*The composite ocular redness score is the sum of ciliary, conjunctival and episcleral vessel bed scores. Each item was rated on a 4- or 5-point scale (0 = no symptom; 3 or 4 = extremely severe). If any one of the three scores was missing, the composite score was set to missing.

[†]*P* values were based on the analysis of variance model containing the fixed effects of treatment, phase, and treatment sequence, and the random effect of subject nested within treatment sequence.

DL, desloratadine; PBO, placebo; CI, confidence interval; SD, standard deviation; SE, standard error.

Discussion

This study found that desloratadine 5 mg once daily reduced post-conjunctival challenge ocular symptom scores in subjects with a history of seasonal AC. Redness scores in two of the three components (ciliary and episcleral vessel beds) were significantly better in desloratadine-treated subjects ($P < 0.05$ for both comparisons).

In addition, the greatest percentage reductions were noted for itching and tearing, symptoms which, according to the Allergies in America survey, are particularly important to individuals with AC [7].

Treatment with desloratadine decreased mean composite ocular redness compared with placebo at all time-points, but this reduction was not statistically significant. Similarly, ciliary and episcleral redness scores were lower

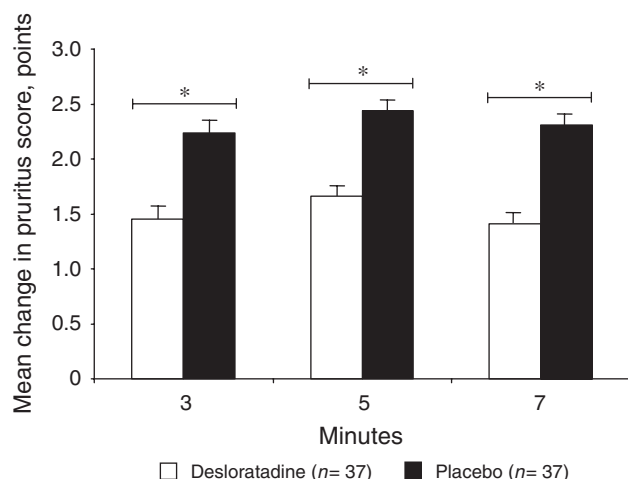


Fig. 2. Mean change from baseline in pruritus score. (* $P < 0.001$).

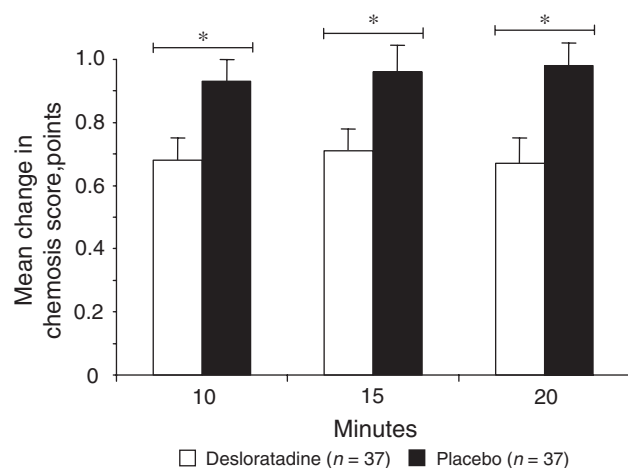


Fig. 3. Mean change from baseline in chemosis score. (* $P < 0.03$).

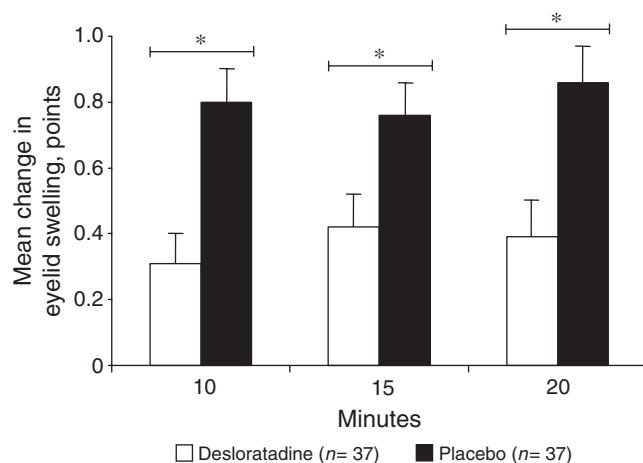


Fig. 4. Mean change from baseline in eyelid swelling. (* $P < 0.03$).

with desloratadine but only reached statistical significance at the 10-min assessment. Ocular redness results in part from vasodilation of the ocular blood vessels via

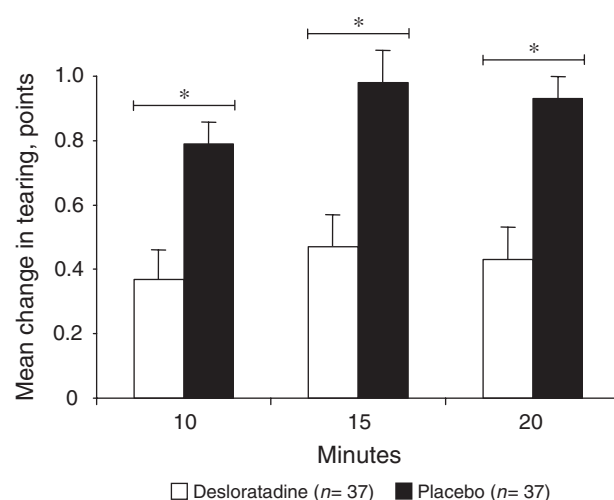


Fig. 5. Mean change from baseline in tearing score. (* $P < 0.003$).

stimulation of H_2 -receptors on the surface of the eye [18]. In one study, the H_2 -receptor antagonist cimetidine was instilled in the left eyes of 10 healthy volunteers, followed by challenge in both eyes with dimaprit dihydrochloride, a highly selective H_2 -receptor agonist [18]. The eyes pretreated with cimetidine had significantly less vasodilation than those that received no pretreatment. In a second challenge 48 h later, vasodilation caused by dimaprit dihydrochloride challenge was not blocked by pretreatment with antazoline phosphate, an H_1 -receptor antagonist. The authors concluded that to completely block vasodilation in the ocular vessel beds, combination therapy with H_1 - and H_2 -receptor antagonists is required.

This study is the first to assess the inhibitory effects of desloratadine on allergen-induced ocular symptoms following CAC using a crossover design. Guidelines recommend regular, as opposed to as-needed, treatment with antihistamines; therefore, study subjects were treated for 7 days before challenge to reproduce the recommended treatment scenario. A number of factors, such as hormonal status and exposure to allergens outside the study, have been shown to influence an individual's allergic response; therefore, we used a crossover design to minimize the influence of patient-dependent and time-dependent variables that could affect study outcomes. In this controlled environment, pretreatment with desloratadine was found to significantly inhibit six distinct markers of ocular allergic response.

The primary reaction of most patients with ocular allergy is acute; thus, we designed this study to parallel the time course of early-phase allergic response [19], assessing ocular redness, chemosis, eyelid swelling, and tearing at 10, 15, and 20 min post-challenge and ocular pruritus at 3, 5, and 7 min post-challenge. A late-phase allergic response can begin 4–8 h after the acute reaction [20]. However, the time course and pattern of symptoms in the late-phase response is highly variable and can be

continuous from time of provocation, intermittent, or classic [21].

Desloratadine was found to exert effects on signs and symptoms of AC. Although these findings attained statistical significance, clinical significance (i.e. a 1.0-U difference in mean scores between the drug treatment and placebo groups) was not achieved. The effects of oral desloratadine on AC may be enhanced by administration of a topical ophthalmic antihistamine, which has previously been shown to be an optimal treatment option when used in combination with a systemic antihistamine [14].

While not focusing solely on ocular symptoms, three large placebo-controlled trials have reported that once-daily desloratadine significantly improved both nasal and non-nasal symptoms, including ocular symptoms, in subjects with AR, as measured in standard phase III pivotal study designs based on total symptoms scores [22–24]. Our study investigated the effects of desloratadine in the standard model by which ocular allergy agents are evaluated. In a 2-week dose-ranging study of 1026 subjects with seasonal AR, significant relief of ocular itching and tearing was noted at all dosing levels (2.5–20 mg once daily) [22]. Significant improvements in ocular symptoms were also reported after 4 weeks of desloratadine 5 mg once daily in a trial of 676 subjects with perennial AR [23]. More recently, Kim et al. evaluated nasal symptoms, non-nasal symptoms, and peak nasal inspiratory flow over 4 weeks in 1179 subjects with perennial AR [24]. Desloratadine administered 5 mg once daily significantly improved all three outcome measures; of note, while this study included itching and tearing in the non-nasal symptom score, changes in the individual symptoms were not reported.

Choice of treatment for seasonal AC varies depending on the presence or absence of concomitant clinical extraocular symptoms [25]. Topical antihistamines effectively relieve ocular symptoms [25], and the newer second-generation oral antihistamines, such as desloratadine, act systemically to reduce the histamine-mediated nasal and ocular symptoms of seasonal AR [22–24]. As topical ophthalmic solutions have displayed clinical significance for the treatment of AC, these drugs should be used in combination with oral therapy, which has been shown to be more effective than systemic antihistamine treatment alone [14].

Conclusion

The non-sedating second-generation antihistamine desloratadine administered 5 mg once daily for 7 days reduced ocular redness and pruritus, chemosis, eyelid swelling, and tearing following a CAC in subjects with a history of seasonal AC and demonstrated an AE profile similar to that of placebo.

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