Combined Analysis of Two Studies Using the Conjunctival Allergen Challenge Model to Evaluate Olopatadine Hydrochloride, a New Ophthalmic Antiallergic Agent With Dual Activity

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• PURPOSE: To evaluate the effectiveness and safety of olopatadine hydrochloride and to determine its optimal concentration and the onset and duration of action for treating allergic conjunctivitis. Olopatadine is a new topical ophthalmic antiallergic agent that demonstrates activity as both an antihistamine and a mast cell stabilizer. Two double-masked, randomized, placebo-controlled, contralateral eye comparison studies were conducted using the conjunctival allergen challenge model.

• METHODS: A total of 169 subjects received 0.05% or 0.1% olopatadine. Study subjects were healthy adult men and women with a history of active allergic conjunctivitis within the previous two seasons but not receiving current treatment. With an allergen dose that produced signs and symptoms of allergic conjunctivitis at visits 1 and 2, the conjunctival allergen challenge was performed 27 minutes after study drug administration at the third visit (onset-of-action challenge) and at 8 hours after study drug administration at the fourth visit (duration-of-action challenge). Olopatadine was administered in one eye and placebo in the opposite eye. Itching and redness were scored for both eyes at 3, 10, and 20 minutes after the conjunctival allergen challenge.

• RESULTS: Both 0.05% and 0.1% concentrations of olopatadine were significantly ($P < .05$) more effective than placebo in inhibiting itching and redness at all evaluations when administered 27 minutes or 8 hours before the conjunctival allergen challenge. There were no serious or drug-related ocular or nonocular adverse events in either study.

• CONCLUSION: These findings demonstrate the rapid and prolonged (at least 8 hours) ocular antiallergic action of olopatadine.

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ALLERGIC CONJUNCTIVITIS IS A CONDITION that occurs seasonally or perennially in response to environmental allergens. Ocular itching is the hallmark symptom of allergic conjunctivitis and is often the most troublesome for the patient.[1] Other symptoms and signs of allergic conjunctivitis include ocular redness, tearing, mucus production, foreign body sensation, chemosis, and lid edema. In its mildest form, the signs and symptoms may be self-limiting.[2] However, often the signs and symptoms of allergic conjunctivitis are

recurrent, waxing and waning, and may be accompanied by other allergic manifestations, such as allergic rhinitis.

Orally administered H_1 antihistamines and other systemic antiallergic agents have little effect on the ocular manifestations of allergies.[1] Instead, topical ophthalmic agents should be prescribed. Currently available topical antiallergic agents include H_1 antihistamines, such as levocabastine (Livostin; CIBA Vision, Duluth, Georgia); H_1 antihistamine-vasoconstrictor combinations, such as antazoline-naphazoline (Vasocon-A; CIBA Vision) and naphazoline-pheniramine (Naphcon-A; Alcon, Fort Worth, Texas); mast cell stabilizing agents, such as cromolyn sodium (Crolom; Baush & Lomb, Tampa, Florida) and lodoxamide (Alomide; Alcon); and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketorolac tromethamine (Acular; Allergan, Irvine, California). Topical corticosteroids are reserved for severe, refractory cases of ocular allergic disease such as vernal or atopic keratoconjunctivitis because these agents can be associated with serious side effects, particularly increased intraocular pressure.[1]

Mast cells, which are abundant in the human conjunctiva,[3] play a central role in the pathogenesis of allergic conjunctivitis. When an airborne allergen, such as pollen, animal dander, or dust, enters the eye of an allergic individual, it traverses the conjunctival epithelium and initiates a chain of events which lead to degranulation of mast cells and release of preformed chemical mediators, including histamine, eosinophil chemotactic factor, and tryptase.[4] In addition, the arachidonic acid biosynthetic pathway is activated, yielding prostaglandins and leukotrienes. During the ocular allergic response there are also documented local elevations in kinins, which are potent vasoactive peptides; leukotrienes C_4 and D_4; and albumin, indicating striking increases in vascular permeability.[4,5] Experimentally, selective stimulation of ocular histamine H_1 receptors results in ocular itching.[6] Selective stimulation of ocular H_2 receptors has been reported to produce vasodilation of conjunctival vessels without itching.[7] However, H_2 stimulation effects are controversial.[8] In a clinical setting, most of the ocular H_1 antihistamines are more effective in relieving ocular itching than redness.[9] Topical mast cell stabilizing agents are less effective in relieving itching.[10]

Olopatadine hydrochloride is a new topical ophthalmic antiallergic agent currently under evaluation for use in treating allergic conjunctivitis. In preclinical testing, olopatadine showed prolonged, selective antihistaminic activity in addition to inhibition of mediator release from human mast cells in vitro.[11] Because of its dual activity as an antihistamine and mast cell stabilizer, it is projected to have both rapid onset and prolonged duration of action.

This report presents the combined analysis of two studies in which the conjunctival allergen challenge test was used to evaluate the effectiveness and safety of olopatadine, to determine its optimal concentration and the onset and duration of action for treating allergic conjunctivitis. The conjunctival allergen challenge is a validated model for studying allergic conjunctivitis. It provides standardized, reproducible results, thereby avoiding the variability in symptoms and signs inherent in the naturally occurring condition.[5,10,12] Study 1 evaluated four concentrations of olopatadine (0.01%, 0.05%, 0.1%, and 0.15%), and study 2 evaluated the two most effective concentrations (0.05% and 0.1%) identified in study 1. The results of a combined analysis for olopatadine concentrations of 0.05% and 0.1% are presented here. Both studies were double-masked, randomized, placebo-controlled contralateral eye comparison studies.

SUBJECTS AND METHODS

BOTH STUDIES ENROLLED ADULT SUBJECTS (18 YEARS of age or older), of either sex and any race, with a history of active allergic conjunctivitis within the previous two seasons but not receiving current treatment with topical or systemic medications. Subjects had to have proven allergies demonstrated by positive results on skin prick, radioallergosorbent test, or conjunctival allergen challenge within the previous 24 months, or demonstrated by a positive skin prick test or radioallergosorbent test at the time of study enrollment.

The presence of any ophthalmic abnormality was cause for exclusion from the study, including a

history of dry eye syndrome, blepharitis, follicular conjunctivitis, iritis, or preauricular lymphadenopathy; bacterial or viral ocular infection; history of ocular herpes virus infection; or history of retinal detachment, diabetic retinopathy, or any potentially progressive retinal disease. Subjects using ophthalmic medications requiring longer than a 1-week washout were not included in the study. Contact lens wear was not permitted within 72 hours before the first visit and during the entire study period. The regular use during the study of any topical ophthalmic solution, including tear substitutes, was prohibited, as was the use of any topical medication within 1 week of the start of the study. Subjects were excluded from the study if they showed symptoms or signs of allergic conjunctivitis (any itching or a score of higher than 1 for redness in any one of the three vessel beds) at each of the baseline examinations at the first, second, or third visits. Furthermore, to remain in the study, enrolled subjects had to have a positive conjunctival allergen test on rechallenge (at the second visit), as demonstrated by a score of at least 2 for itching and at least 2 for redness in one or more of three vessel beds (ciliary, episcleral, and conjunctival). Criteria for scoring of ocular symptoms and signs are listed in the Appendix.

Other exclusion criteria were as follows: presence of any significant illness that could interfere with the study, particularly an autoimmune disease such as rheumatoid arthritis, which can be associated with dry eye syndrome; history of cardiovascular, hepatic, or renal disease, with the exception of controlled hypertension; known alcohol or drug abuse; use of any systemic medication that could interfere with the study, including monoamine oxidase inhibitors, nonsteroidal anti-inflammatory agents, mast cell stabilizers, antihistamines, or corticosteroids; use of an oral or topical investigational drug or device within 30 days before receipt of study medication; history of allergy or sensitivity to any ophthalmic drug, including preservatives; and pregnancy or lactation. Women of childbearing potential were required to have a negative pregnancy test before entering the study and to use adequate birth control during the study. All prohibited systemic medications were to be discontinued 72 hours before the start of the study and not used throughout the study.

The experimental design was similar for studies 1 and 2. Both were randomized, double-masked, placebo-controlled, parallel group studies using a contralateral eye comparison. Both studies enrolled adult outpatients at a single center. The first visit served as the screening visit and also, for subjects who fulfilled initial eligibility requirements, as the occasion to identify an antigen and dose that elicited a positive response on the conjunctival allergen challenge. A confirmatory conjunctival allergen challenge was performed at the second visit, which was to occur within 30 days of the first visit in study 1 and within 5 to 9 days of the first visit in study 2. The onset-of-action challenge was performed during the third visit and the duration-of-action challenge was performed during the fourth visit. In the onset-of-action challenge, allergen was instilled 27 minutes after instillation of the study medication. In the duration-of-action challenge, allergen was instilled 8 hours after instillation of the study medication. These time frames were chosen based on preclinical data.[11] For onset-of-action, these data suggest that, while the antiallergic activity of olopatadine begins within minutes of use, its peak activity would be most evident when evaluated 30 minutes after instillation. Therefore, the allergen was instilled at 27 minutes after instillation of olopatadine, with the first evaluation point 3 minutes thereafter. The third visit was scheduled 14 days after the second visit in both studies, and visits 3 and 4 were separated by 7 ± 2 days in study 1 and 14 days in study 2.

Enrolled subjects were randomly assigned to receive 0.05% or 0.1% olopatadine in one eye and placebo (vehicle for olopatadine) in the contralateral eye in a masked fashion. Assignment of the eye to receive active medication was random.

Ophthalmic examinations were performed during the screening visit and at the start of subsequent visits. Ophthalmic examinations included vision assessment (best corrected on Snellen chart), scoring of ocular itching, and slit-lamp examination to assess conjunctival redness, cornea, anterior chamber, and iris. In addition, funduscopy was performed at screening. Pupil size was recorded at the third visit of study 1 at the baseline examination and just

before the conjunctival allergen challenge. In study 2, measurement of pupil size was performed at the baseline ophthalmic examination for each visit and just before the conjunctival allergen challenge on the third and fourth visits.

On the second visit and subsequent visits, any subject showing signs of allergic conjunctivitis (redness score of greater than 1 or any itching) at baseline was asked to return for another visit within 1 week. At all visits, subjects with positive reactions to the conjunctival allergen challenge received, upon request, one or two drops of an ophthalmic antiallergic agent for relief of symptoms when the evaluation period had ended.

Study protocols were designed in accordance with the tenets of the Declaration of Helsinki and approved by the appropriate Institutional Review Board. Written informed consent was obtained from each subject after the nature and possible consequences of the study were explained.

During the first visit, a complete medical history was recorded and the screening examination was done. After providing written consent, subjects who fulfilled entry criteria underwent a pregnancy test (female subjects of childbearing potential), a complete ophthalmic examination, and a skin prick or radioallergosorbent test (those subjects without documented positive response to allergy testing within the prior 24 months).

A bilateral conjunctival allergen challenge titration test was then conducted to determine the appropriate allergen and dilution for subsequent tests. Each subject was challenged with weeds, grasses, trees, or animal dander based on previously documented allergic sensitivity. One 25-μl drop of the lowest dilution (19 allergen units [AU] per 25 μl) of the chosen allergen was administered into each eye. If no reaction occurred within 10 minutes, increasing concentrations of allergen were administered every 10 minutes until a positive reaction was elicited. A positive reaction upon conjunctival allergen challenge was defined as a score of at least 2 for redness and 2 for itching 5 to 10 minutes after allergen administration. If the subject tested negative with the first allergen, another allergen was administered in the same manner. The dilution and type of allergen that elicited a positive response was used for subsequent conjunctival allergen challenge tests. Subjects who failed to respond to any of the allergens were excluded from the study.

A confirmatory conjunctival allergen challenge was performed during the second visit, with the final allergen and dilution that elicited a score of at least 2 for redness and itching at the first visit. Redness of each of three vessel beds and itching were scored and recorded at 3, 10, and 20 minutes after conjunctival allergen challenge. If a redness score of at least 2 in at least one vessel bed and an itching score of at least 2 were present at least at one time point, the subject was deemed eligible for the study.

The onset of drug action was evaluated at the third visit in both studies. Subjects were randomized to receive one drop of olopatadine (at a concentration of 0.05% or 0.1%) in one eye and one drop of placebo in the other eye according to the randomization for treatment arm and eye. The concentration of allergen determined at the first visit and confirmed at the second visit was used for the challenge. Pupil size was recorded immediately before the conjunctival allergen challenge. The conjunctival allergen challenge was performed 27 minutes after study drug instillation. The signs and symptoms of allergic conjunctivitis were scored, as previously described, at 3, 10, and 20 minutes after allergen administration.

The duration of drug action was evaluated at the fourth visit in both studies. Subjects received one drop of olopatadine solution in one eye and one drop of placebo in the opposite eye. The concentration of allergen determined at the first visit and confirmed at the second visit was used for the challenge. The conjunctival allergen challenge was performed 8 hours after study drug instillation in both studies. In study 2, the conjunctival allergen challenge was performed immediately after taking the pupil size measurement. Itching and redness were then scored at 3, 10, and 20 minutes after the conjunctival allergen challenge. Subjects completed an exit form and all female subjects of childbearing potential underwent a pregnancy test at the end of the final visit.

The conjunctival allergen challenge was conducted using one of four common allergens, namely, grasses, weeds, animal dander, or trees: Kentucky bluegrass (*Poa pratensis*); short ragweed (*Ambrosia artemisiifolia*); cat dander (*Felis domesticus*); and elm

TABLE 1. Patient Demographics

	Olopatadine		All Subjects
	0.05%	0.1%	
No. of subjects	84	85	169
Sex (no. [%])			
Male	30 (36)	33 (39)	63 (37)
Female	54 (64)	52 (61)	106 (63)
Age (yrs)			
Mean	39	38	39
Range	18–80	19–75	18–80
Race (no. [%])			
White	77 (92)	79 (93)	156 (92)
Black	1 (1)	2 (2)	3 (2)
Asian	0 (0)	1 (1)	1 (1)
Other	6 (7)	3 (4)	9 (5)
Iris (no. [%])			
Brown	30 (36)	38 (45)	68 (40)
Blue	22 (26)	16 (19)	38 (22)
Hazel	4 (5)	9 (11)	13 (8)
Green	28 (33)	22 (26)	50 (30)

(*Ulmus americana*). Serial dilutions were made from allergen stock solutions containing 100,000 AU per mL, resulting in seven test dilutions ranging from 19 to 1250 AU per 25-μl dose of allergen. Phosphate-buffered saline solution was used as the diluent. Olopatadine ophthalmic solution and placebo (vehicle for olopatadine ophthalmic solution) were supplied by Alcon Laboratories.

Safety assessments of olopatadine for studies 1 and 2 included recording of both spontaneous and solicited adverse events throughout the study periods. Adverse events were defined as any changes from baseline in a subject's ophthalmic or medical health. The onset, duration, severity, and outcome of each adverse event were recorded. Serious adverse events were noted, and the relation of all adverse events to study drug administration was classified as definitely unrelated, unlikely, possible, probable, or definitely related. Serious events were defined as events that caused or prolonged hospitalization, were life- or sight-threatening, or were fatal or permanently disabling. In addition, a congenital anomaly, cancer, or overdose was defined as a serious adverse event.

A sign rank test was used to compare the primary efficacy variables, itching and redness, for each concentration of olopatadine with contralateral placebo (paired sample) at each evaluation time after the conjunctival allergen challenge. The sum of scores for ciliary, conjunctival, and episcleral redness was used for the redness scoring.

SAS version 6.1 (SAS Institute, Cary, North Carolina) was used for all calculations. Summary statistics were provided for each of the variables in the analyses. All hypothesis tests were conducted with a 0.05 probability of a type 1 error.

RESULTS

STUDY 1 EVALUATED FOUR CONCENTRATIONS OF OLopatadine (0.01%, 0.05%, 0.1% and 0.15%). In preclinical tests, an olopatadine concentration of 0.01% was the minimum effective dose, producing a 50% inhibition (EC_{50}) of histamine-stimulated vascular permeability in guinea pig conjunctiva when used at least 15 minutes before challenge. The EC_{50} concentrations at 8 and 24 hours were 0.04% and 0.11%, respectively.[11] A concentration of 0.15% represents the upper limit of solubility of olopatadine. Study 2 evaluated two concentrations of olopatadine (0.05% and 0.1%). Because the 0.01% and 0.15% concentrations were not the strongest candidates for a clinical formulation, and for ease of comparison of data, findings presented here from study 1 include only those for the 0.05% and 0.1% concentrations.

A total of 169 subjects was enrolled in the two studies. Of those, 84 subjects were randomly assigned to receive 0.05% olopatadine, and 85 subjects were randomly assigned to receive 0.1% olopatadine. Demographic data and eye color were similar for the two treatment groups. The mean age of study subjects was 38 years (range, 18 to 80 years). A tabular summary of demographic data for both studies combined is presented in Table 1.

All subjects in both studies received drug and were evaluable for the safety analyses. The efficacy analyses for the 27-minute and 8-hour conjunctival allergen challenges included those subjects who completed that particular visit. One subject in the 0.05% olopatadine treatment group missed the third visit (onset-of-action challenge), and one subject in the 0.1% olopatadine treatment group was not evaluable at the fourth visit (duration-of-action

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