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Efficacy of Once-Daily Olopatadine 0.2% Ophthalmic Solution Compared to Twice-Daily Olopatadine 0.1% Ophthalmic Solution for the Treatment of Ocular Itching Induced by Conjunctival Allergen Challenge

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ABSTRACT Olopatadine 0.1% (Patanol®) and olopatadine 0.2% (Pataday™) ophthalmic solutions are topical ocular anti-allergic agents with antihistaminic and mast cell stabilizing properties. The efficacy of two doses of olopatadine 0.1% was compared to one dose of olopatadine 0.2% in the prevention of ocular itching associated with allergic conjunctivitis over 24 hours. This double-masked conjunctival allergen challenge (CAC) study found no significant difference in the mean itching scores between two drops of olopatadine 0.1% and one drop of olopatadine 0.2%. Both showed significant activity at the 24-hour time point and were statistically superior to placebo. No adverse events occurred while on drug therapy.

KEYWORDS olopatadine; conjunctival allergen challenge; ophthalmic; allergic conjunctivitis; rhinoconjunctivitis; allergy; Pataday; Patanol

INTRODUCTION

The allergic response occurs secondary to crosslinking of allergens to IgE molecules on sensitized mast cells. This triggers degranulation of the mast cell and subsequent release of various allergic and inflammatory mediators. All of these mediators contribute to the allergic reaction; however, histamine plays the primary role, particularly in initiating ocular itching.[1–4]

Treatment options are available to help ease these symptoms by stabilizing mast cells as well as blocking histamine binding to ocular H_1 receptors. Olopatadine 0.1% (Patanol,® Alcon), for example, is a potent H_1 antihistamine[5] and a proven human conjunctival mast cell stabilizer.[6]Patanol® is indicated for the twice-daily treatment of all signs and symptoms of allergic conjunctivitis. It has consistently been shown to be comfortable and well tolerated; its safety has been investigated extensively in both adults and children.[7–11]

Olopatadine 0.2% (Pataday,™ Alcon) is a new formulation of olopatadine that was developed to enhance clinical efficacy by extending the duration of action. Olopatadine 0.2% contains twice the active molecule as olopatadine 0.1%. The excipients of the two formulations are similar, with the addition of edetate disodium (EDTA) and povidone to olopatadine 0.2%. EDTA is a common chelating agent that was added to enhance the preservative efficacy of the new formulation. Povidone, a common ingredient in many ophthalmic products, is an FDA-classified demulcent. Olopatadine 0.2% is indicated once daily for the treatment of ocular itching associated with allergic conjunctivitis. In clinical trials it has been shown to significantly reduce ocular itching and redness associated with allergic conjunctivitis.[12,13] It has also demonstrated an extended duration of action of up to 24 hours.[13] Olopatadine 0.2% has been shown to be safe in both adults and children as young as three years of age,[14] and its once-daily dosing regimen increases convenience and compliance for all ocular allergy patients.

This study used the conjunctival allergen challenge (CAC) model to compare the efficacy after 24 hours of one dose of olopatadine 0.2% to two doses (separated by 8 hours) of olopatadine 0.1% in the prevention of ocular itching associated with allergic conjunctivitis. The CAC model employed in this study used titrated quantities of allergen to induce the signs and symptoms of allergic conjunctivitis in a standardized, precise, and reproducible manner. Pre-determinded concentrations of allergen are used to elicit an allergic response, eliminating much of the variability associated with environmental models.[15] The method allows for evaluation of safety, comfort, and efficacy using standardized grading scales.

METHODS

Design

This was a 3-week, double-masked, randomized, contralateral eye, placebo-controlled CAC study. The study visits were conducted in a clinic setting (Ophthalmic Research Associates, North Andover, MA), and all study-related procedures and ophthalmic examinations were conducted by examiners who were qualified through medical training and experience with the CAC methodology. The study protocol, informed consent form, investigator qualifications, and all recruiting materials were approved by an independent institutional review board (IntegReview, Austin, TX) prior to initiation of the study. The study was conducted in accordance with current Good Clinical Practice guidelines and the Declaration of Helsinki.

Visit 1: Baseline Screening (Day-14 $\pm$ 3)

Written informed consent was obtained from each subject. The study followed a standardized allergen challenge protocol.[15] Demographic data, along with medical and medication histories were recorded, and visual acuity was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart. A urine pregnancy test was administered to women of childbearing potential. Subjects were not allowed to use any topical ocular medication (other than study medication) for the duration of the study, have any active ocular disease, or use any systemic medication that could have affected the outcome of the study (e.g., topical or systemic antihistamines, mast cell stabilizers, corticosteroids).

A biomicroscopic (slit lamp) examination was performed to exclude all subjects with disallowed ocular conditions, including erythema (redness), defined as a redness score of >1 in any ocular vessel bed (ciliary, conjunctival, episcleral). In addition, any subject who experienced any itching in either eye at baseline was excluded. A CAC was performed bilaterally with an allergen to which the subject tested positive in a skin prick test (e.g., cat dander, trees, ragweed, or grasses). Skin prick tests were performed within 24 months of study initiation, and were used as inclusion criteria. Increasing antigen concentrations were instilled bilaterally at 10-min intervals until a positive reaction was elicited. Ocular itching was assessed using a scale that ranged from 0 to 4, where 0 = no itch and 4 = incapacitating itch; redness was assessed using a 0 to 4 scale, where 0 = no redness and 4 = "extremely severe" redness. A positive CAC reaction was defined as a score of ≥ 2 for redness in at least one of the three vessel beds of each eye and ≥ 2 for ocular itching in both eyes within 10 min of receiving that dose of allergen. Any subject who failed to test positively was excluded from the study.

Visit 2: Confirmatory (Day-7 $\pm$ 3)

Medical and medication histories were updated and visual acuity was recorded. A biomicroscopic

examination was performed to exclude subjects with active allergic conjunctivitis (a score of >1 for redness in any vessel bed or any itching in either eye) at baseline. A second CAC was administered to each subject using the same antigen/concentration combination that elicited the positive reaction at Visit 1. The subject made assessments of ocular itching at 3, 5, and 7 min following allergen challenge. The investigator made assessments of redness at 7, 15, and 20 min post-challenge. If the subject failed to react positively (i.e., ≥2 for redness in at least one vessel bed and ≥2 for itching) in both eyes in at least one out of the three time points within this 20-min interval, the subject was discontinued from the study.

Test Visit: Drug Evaluation (Day 0, one Week After Visit 2)

Medical and medication histories were updated and visual acuity was recorded. A biomicroscopic examination was performed to exclude subjects with active allergic conjunctivitis (a score of >1 for redness in any vessel bed or any itching in either eye) at baseline. Baseline allergic signs and symptoms were assessed.

Subjects who continued to qualify for the study were assigned treatment numbers in sequential order and had one drop of masked study medication instilled in the conjunctival sac of the appropriate eye according to a prescribed randomization schedule. Prior to commencement of all study procedures, an independent statistician who was not involved in any other aspect of the study developed the randomization schedule. Subjects were randomized by eye into treatment groups in a 1:1:1 pattern to receive olopatadine 0.2%, olopatadine 0.1%, or placebo (Tears Naturale II®) (Table 1). Given the bilateral symmetry of the ocular allergic response during the CAC, contralateral, placebo-controlled treatment arms were used in this study, allowing the subject to act as an internal control.[15–17] A similar study design was used for the pivotal study of olopatadine 0.1%.[18] For patient distribution into study groups, see Table 2.

All subjects received a second dose of masked study medication 8 hours after the first (Table 1). Twenty-four hours after the first dose, a conjunctival allergen challenge was performed bilaterally using the same concentration of allergen that had elicited a positive response at Visits 1 and 2. Ocular assessments of itching were performed in the same manner and at the identical time points as described for Visit 2. Adverse events were collected for all subjects post-instillation of study drug. A final visual acuity and slit lamp exam was conducted for all subjects.

TABLE 1 Patients were randomized by eye to receive olopatadine 0.2%, olopatadine 0.1%, or placebo at the first and second dose

First dose	Second dose
Olopatadine 0.2% in one eye and placebo in the other	Placebo in both eyes
Olopatadine 0.1% in one eye and placebo in the other	Olopatadine 0.1% in same eye and placebo in the other
Olopatadine 0.2% in one eye and olopatadine 0.1% in the other	Placebo in the eye that had olopatadine 0.2% and olopatadine 0.1% in the other eye
Olopatadine 0.2% in both eyes	Placebo in both eyes
Olopatadine 0.1% in both eyes	Olopatadine 0.1% in both eyes
Placebo in both eyes	Placebo in both eyes

Statistical Analyses

Statistics & Data Corporation of Mesa, Arizona, performed statistical analyses. Non-parametric Wilcoxon rank sum tests were performed on the mean scores per eye at each time point to assess statistical significance in the differences between treatments. The primary efficacy variable in this study was ocular itching. Statistical significance was defined as $\alpha = 0.05$. Safety was evaluated through a review of all reported adverse events. Changes from baseline in visual acuity and slit lamp biomicroscopy were reviewed for clinical

TABLE 2 Patients ($N = 23$) were distributed among nine possible treatment combinations

Number of subjects	OD Treatment	OS Treatment
3	Olopatadine 0.2%	Placebo
3	Olopatadine 0.1%	Placebo
3	Placebo	Olopatadine 0.2%
2	Placebo	Olopatadine 0.1%
2	Placebo	Placebo
3	Olopatadine 0.2%	Olopatadine 0.1%
3	Olopatadine 0.1%	Olopatadine 0.2%
2	Olopatadine 0.2%	Olopatadine 0.2%
2	Olopatadine 0.1%	Olopatadine 0.1%

significance. No statistical analyses were performed to evaluate safety.

RESULTS

Subject Disposition

Of the 37 screened subjects, 23 were enrolled based on the inclusion/exclusion criteria. All 23 enrolled subjects completed the study. Subject demographics are shown in Table 3.

Efficacy

At the 24-hour time point, two doses of olopatadine 0.1% significantly reduced itching scores in comparison to placebo ($p = 0.002$). Similarly, one dose of olopatadine 0.2% significantly reduced itching scores in comparison to placebo ($p = 0.0007$). Both treatments demonstrated 1-score unit differences from baseline. There were no statistically significant differences (Fig. 1) in the mean itching reduction scores between olopatadine 0.1% dosed twice daily (BID) and olopatadine 0.2% dosed once daily (QD) ($p = 0.081$) at 24 hr.

Safety

No adverse advents occurred while on drug therapy. Olopatadine 0.2% and olopatadine 0.1% were both found to be safe and well tolerated as used in this study. No clinically significant changes from baseline for visual acuity or slit-lamp biomicroscopy safety measurements occurred for either drug formulation. Slit-lamp biomicroscopy examinations included lids, tear meniscus, conjunctiva, cornea, lens, and anterior chamber. Any abnormalities or changes from baseline would have been noted as adverse events.

TABLE 3 Demographics of the 23 subjects enrolled in the study

Sex, *N* (%)	
Female	13 (56.5)
Male	10 (43.5)
Age (years), mean	41
Race, *N* (%)	
Caucasian	22 (95.7)
Hispanic	1 (4.3)
Iris color, *N* (%)	
Brown	9 (39.1)
Hazel	7 (30.4)
Blue	5 (21.7)
Green	2 (8.7)

DISCUSSION

Ocular itching associated with allergic conjunctivitis is a constant source of irritation for many people. Olopatadine 0.1% has been prescribed as an effective twice-daily antihistamine/mast cell stabilizer for treating allergic conjunctivitis.[11,16–17] The increasing prevalence of allergies combined with patient attitudes towards usage has prompted an increased need for once-daily treatments.[19] Olopatadine 0.2% is an ocular antiallergy agent indicated for once-daily dosing. A one-drop dose has a rapid onset of action and provides quick relief from allergy symptoms–relief that is sustained for 24 hours.

Using the CAC model, this study showed that over 24 hours, one drop of olopatadine 0.2% has an efficacy profile comparable to two drops of the original formulation. Since the two formulations share the indication for the relief of ocular itching, this was the variable analyzed. These results are consistent with previous studies performed with the olopatadine molecule,

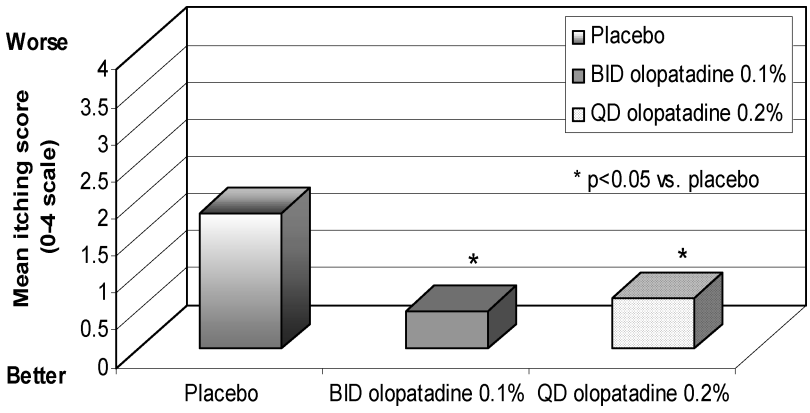

FIGURE 1 Comparison of mean ocular itching scores between olopatadine 0.2%, olopatadine 0.1%, and placebo following conjunctival allergen challenge performed 24 hours after medication instillation ($N = 23$).

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