Efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution Compared With Placebo in the Conjunctival Allergen Challenge Model

Mark B. Abelson, MD; Matthew J. Chapin, BS; Barry M. Kapik, MS; Naveed B. K. Shams, MD, PhD

Background: Ketotifen fumarate blocks histamine (H1) receptors, stabilizes mast cells, and acts as an eosinophil inhibitor (decreases chemotaxis and activation of eosinophils).

Objective: To assess the efficacy of ketotifen 0.025% ophthalmic solution in the prevention of symptoms of allergic conjunctivitis, using the conjunctival allergen challenge model.

Methods: This was a single-center, double-masked, randomized, placebo-controlled, contralateral-eye comparison, allergen challenge trial conducted in the United States. Subjects were randomized to receive ketotifen 0.025% in one eye and placebo in the other. At visits 1 and 2, allergen challenges were performed to determine the allergen concentration eliciting a qualifying reaction for each subject. At the 3 subsequent visits, subjects received 1 drop of ketotifen 0.025% ophthalmic solution in one eye and vehicle solution as placebo in the other eye 15 minutes (visit 3), 6 hours (visit 4), and 8 hours (visit 5) before allergen challenge. The primary efficacy measure was the subject’s rating of itching at 3, 7, and 10 minutes after challenge.

Results: Of the 89 subjects randomly assigned to masked trial medication at visit 3, 72 completed the study. At visits 3, 4, and 5, mean itching scores were significantly better for ketotifen-treated eyes at all postchallenge time points, compared with placebo (P<.001). Also at visits 3, 4, and 5, ketotifen was statistically superior to placebo in reducing ocular hyperemia at all postchallenge time points (P<.05).

Conclusions: Ketotifen was safe and statistically effective in reducing ocular itching and hyperemia associated with allergic conjunctivitis. Ketotifen’s rapid onset of action (within 15 minutes) and extended duration of action (at least 8 hours) make it a valuable treatment for allergic conjunctivitis.

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The prevalence of ocular allergic disease, which comprises several conditions, is estimated to be 20% and increasing. Seasonal allergic conjunctivitis is the most common type of ocular allergy and may account for up to 90% of all allergic eye disorders seen by the allergist. Common ocular signs and symptoms associated with seasonal allergic conjunctivitis are itching, tearing, swelling, and conjunctival, episcleral, and ciliary redness. Although vision is not impaired by seasonal allergic conjunctivitis, the symptoms can be uncomfortable and may substantially affect quality of life.

There are 5 major drug classes used to treat ocular allergies: antihistamines (levocabastine hydrochloride and emedastine difumarate), mast cell stabilizers (cromolyn sodium, nedocromil sodium, pemirolast potassium, and lodoxamide tromethamine), antihistamine and mast cell stabilizer combinations (ketotifen fumarate, azelastine hydrochloride, and olopatadine hydrochloride), corticosteroids (loteprednol etabonate), and nonsteroidal anti-inflammatory drugs (ketorolac tromethamine). Ketotifen (Zaditen and Zaditor, Novartis Ophthalmics, Inc) is one of the more recently developed agents that has multiple pharmacological mechanisms. It is a benzcycloheptathiophene derivative that has been developed for the treatment of allergic conjunctivitis. Ketotifen is a noncompetitive histamine (H1)–receptor antagonist that stabilizes mast cells, inhibits platelet-activating factor, and acts as an eosinophil inhibitor (decreases chemotaxis and activation of eosinophils). The aim of this study was to evaluate the efficacy of ketotifen 0.025% ophthalmic solution compared with placebo in the prevention of symptoms of allergic con-
junctivitis, using the conjunctival allergen challenge model.\(^5\) The approval of ketotifen 0.025% by the US Food and Drug Administration was based on 2 allergen challenge studies\(^7,8\) and 1 large, repeated dose safety study (M.B.A, Steven Dell, MD, George Lowry, MD, David G. Shulman, MD, and Francis J. Wapner, MD, unpublished data, 1998). Data contained in the article come from 1\(^7\) of the 2 allergen studies conducted for the registration of ketotifen.

### METHODS

#### SELECTION OF STUDY POPULATION

Subjects were aged 18 to 70 years, with a history of allergic hypersensitivity to animal dander, grass, or tree or ragweed pollen not currently in season in the site's geographic area. The principal eligibility criterion for study enrollment was a positive diagnostic test result (skin or radioallergosorbent test) for allergic hypersensitivity or a positive allergen challenge within 24 months of visit 1. Subjects must also have had a qualifying allergic reaction, inducing at least 2+ itching and 2+ conjunctival redness bilaterally within 10 minutes after challenge at visits 1 and 2. Further criteria were best-corrected distance visual acuity of 20/40 (logMAR 0.3) or better in both eyes on an Early Treatment of Diabetic Retinopathy Study chart, intraocular pressure of 21 mm Hg or less in both eyes, and ability and willingness to provide written and informed consent. Women of childbearing potential had to use an adequate form of birth control (for at least 1 month before visit 1) and produce a negative urine pregnancy test result at visit 1. Exclusion criteria included the following: history of any retinal condition or disease; active bacterial or viral ocular infection; signs and symptoms of allergic conjunctivitis; presence of an interacting ocular condition (such as blepharitis, follicular conjunctivitis, and open- or narrow-angle glaucoma); or any physical illness that would make the subject unsuitable. Use of systemic or ocular medication, such as monoamine oxidase inhibitors, antihistamines, or mast cell stabilizers, or participation in an investigational drug or device trial within the previous 30 days before the trial was prohibited. The trial was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.

#### STUDY DESIGN

This was a single-center, double-masked, randomized, placebo-controlled, contralateral-eye comparison, allergen challenge trial conducted in the United States. Subjects were randomized to receive ketotifen 0.025% in one eye and placebo in the other eye at 3 visits. A randomization list was prepared by the sponsor, using computer software (PROC PLAN, SAS version 6.12; SAS Institute Inc, Cary, NC).

The study involved 5 visits, with a 2-week screening that included ophthalmic examinations at visits 1 (day −21) and 2 (day −14). The screening also included allergen challenges at both visits to determine the allergen type and concentration eliciting a qualifying reaction for each subject. Allergen responses were determined by the investigator for each subject at visit 1, starting with the lowest dose and titrating to the highest dose until a qualifying reaction was achieved bilaterally. Allergens included ragweed pollen (36 [42%] of 86 subjects), meadow fescue pollen (21 [24%] subjects), cat dander (16 subjects), rye pollen (9 [10%] subjects), and tree pollen (7 [8%] subjects). This study was conducted outside of the pollen season, and the enrolled subjects were required to have either no allergy signs and symptoms at the time of testing or had no more than mild redness and itching.

At visits 3, 4, and 5, subjects received 1 drop of ketotifen 0.025% ophthalmic solution into the conjunctival sac of one eye and placebo as vehicle solution in the other eye 15 minutes (visit 3), 6 hours (visit 4), and 8 hours (visit 5) before allergen challenge. After visit 2, there was a 14-day recovery period between subsequent visits.

To help maintain masking, the packaging of ketotifen and placebo was identical in appearance. All products were supplied in 3-mL plastic dropper bottles for ocular administration.

#### OUTCOME MEASURES

The primary efficacy measure was the subject's rating of itching at 3, 7, and 10 minutes after the allergen challenge. Secondary efficacy measures were the investigator's ratings of conjunctival, episcleral, and ciliary hyperemia at 7, 10, and 15 minutes after the allergen challenge.

Ocular itching, hyperemia, and chemosis were measured on a 5-point grading scale from 0 (none) to 4 (severe), and lid edema was measured on a 4-point scale from 0 (none) to 3 (extremely swollen). The primary and secondary efficacy variables were the between-treatment (interocular) differences. For primary and secondary efficacy outcomes, a clinically meaningful difference was defined as a mean difference score of at least 1.0 U between treatment groups at 2 of the 3 time points.

Safety was assessed by evaluating changes in visual acuity (on an Early Treatment of Diabetic Retinopathy Study chart), slitlamp biomicroscopy and dilated ophthalmoscopy results, and tabulating reports of adverse events.

#### STATISTICAL ANALYSIS

For ocular signs and symptoms, it was estimated that a sample size of 80 subjects would provide at least 98% power to detect a between-group difference of 0.3, assuming a 2-sided \( \alpha \) of .05 and an SD of 1.07 (paired \( t \) test). The estimate of the SD was obtained from a previous study\(^8\) comparing ketotifen with its vehicle placebo in an allergen challenge model.

The primary efficacy analysis was performed on the intent-to-treat subjects, defined as those who received drug and had at least 1 efficacy assessment. For itching and hyperemia scores, paired \( t \) tests on the difference scores between eyes were used to assess differences between treatments at each visit. The percentage of eyes with no itching was compared between treatment groups using the McNemar test for matched pairs. All statistical tests were 2-sided, and corresponding differences were considered statistically significant at \( P < .05 \).

#### RESULTS

Eighty-nine subjects were randomly assigned to masked trial medication and received 1 or more doses of each medication (Figure 1). Seventy-two subjects (81%) completed the study. Of the 17 subjects who did not complete the study, 8 were lost to follow-up, 3 discontinued voluntarily, 5 were discontinued for protocol violations, and 1 left for other reasons. Fifty-four percent (48/89) were male, and 93% (83/89) of the subjects were white. The mean age was 38.9 years (range, 19-70 years). Two (2%) subjects had black iris color; 35 (39%), brown; 23 (26%), hazel; and 29 (33%), blue. Only 2 (2%) subjects had a history of ocular surgery. There were no significant differences between the treatment groups at baseline for ocular itching or hyperemia.


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Efficacy

Ocular Itching

For visits 3, 4, and 5, mean itching scores after allergen challenge were statistically significantly different between treatment groups, favoring ketotifen-treated eyes at all time points after allergen challenge (P<.001) (Table 1 and Figure 2). Mean differences in itching scores between ketotifen-treated eyes and eyes that received placebo ranged from −1.16 to −1.80 U. The percentage of ketotifen-treated eyes with no itching was also significantly higher than the corresponding percentage of eyes given placebo at all time points (P<.001) (Table 2). These differences between groups ranged from 52% to 61%. Subgroup analyses revealed no significant differences attributable to sex or iris color.

Hyperemia

Ketotifen was statistically superior to placebo at every time point in reducing the effect of the allergen challenge on ocular hyperemia; ketotifen-treated eyes had significantly lower mean scores compared with eyes given placebo (P<.05) (Table 3). At visit 3 (15-minute challenge), mean differences between the treatments ranged from −0.52 to −0.76 U.

Safety

There were no statistically significant differences between treatments for prechallenge and postchallenge assessments of slitlamp or direct ophthalmoscopy findings.

One or more adverse events were reported by 13 (15%) of the 89 subjects, but none were ocular in nature. The most frequently occurring adverse events reported by subjects were headache (6 or 7%) and rhinitis (3 or 3%). The only adverse event considered by the investigator to be associated with study treatment was headache, reported by 4 (5%) of 89 subjects.

There were no reports of serious or severe adverse events, and no individuals discontinued prematurely because of adverse events.

Comment

This clinical study shows that ketotifen 0.025% ophthalmic solution can achieve statistically significant prevention of the development of itching due to allergic conjunctivitis, starting within 15 minutes of treatment and lasting for at least 8 hours. The beneficial effects of ketotifen on itching are supported by the results of the mean itching scores, as well as the proportion of eyes without any itching. These findings are clinically meaningful, as ketotifen provides a rapid onset and long duration of ac-

<table>
<thead>
<tr>
<th>Assessment Time After Challenge, min</th>
<th>Visit 2 (n = 89)</th>
<th>Visit 3 (n = 89)</th>
<th>Visit 4 (n = 83)</th>
<th>Visit 5 (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.02 (0.48)</td>
<td>−1.41 (1.02)</td>
<td>−1.43 (1.10)</td>
<td>−1.16 (1.06)</td>
</tr>
<tr>
<td>7</td>
<td>0.04 (0.40)</td>
<td>−1.80 (1.16)</td>
<td>−1.54 (1.01)</td>
<td>−1.41 (0.95)</td>
</tr>
<tr>
<td>10</td>
<td>0.03 (0.35)</td>
<td>−1.39 (1.01)</td>
<td>−1.33 (0.97)</td>
<td>−1.26 (0.92)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) difference between eyes. A negative difference indicates a better outcome for ketotifen-treated eyes.
tion. Ketotifen was also safe and well tolerated, an important finding given that compliance with ophthalmic formulations is enhanced by a favorable tolerability profile.9

Higher mean scores for conjunctival, ciliary, and episcleral hyperemia for all time points at visits 3, 4, and 5 were recorded for eyes given placebo. Although the treatment effect of ketotifen on ocular hyperemia was not as marked as for itching, the intensity of hyperemia was suppressed enough to achieve statistical significance at all time points. In allergic conjunctivitis, histamine induces itching through H1 receptors and hyperemia through H2 and H3 receptors.10,11 Ketotifen’s smaller treatment benefit on hyperemia may therefore reflect its relative selectivity for H1 receptors.

The advantages of using the allergen challenge model in evaluating the antiallergy effects of pharmacological agents have been reviewed previously.6,12 Unlike other models, the allergen challenge model accurately replicates the signs and symptoms and natural disease process of seasonal allergic conjunctivitis. In addition, it is safe and reproducible and can be used to accurately determine the duration of action, on which the dosing frequency can be based. In contrast to environmental studies, a small sample size can be used for allergen challenge studies, especially in the case of contralateral-eye designs. The model has been used to evaluate several ophthalmic formulations, such as ketorolac,13 levocabastine and emedastine,14 and olopatadine.15 Furthermore, it is able to detect differential effects between active treatments and placebo, as well as differences in efficacy between active treatments.

Ketotifen modulates early-phase reactions by blocking H2 receptors, stabilizing mast cells, and acting as an eosinophil inhibitor (decreases chemotaxis and activation of eosinophils).16 Moreover, ketotifen inhibits late-phase reactions on a cellular level, such as reducing the effect of platelet-activating factor.17 The multiple mechanisms of action of ketotifen would be expected to provide rapid and prolonged relief of ocular symptoms in patients with allergic conjunctivitis. The results from this study provide support for these effects. In clinical practice, ketotifen’s prolonged symptom relief translates into a twice-daily regimen, which may result in increased treatment compliance, thus leading to effective control of ocular symptoms associated with allergic conjunctivitis.

In this study, safety and local tolerability of ketotifen 0.025% ophthalmic solution was assessed following the single administration of the drug at visits 3, 4, and 5. No ocular adverse effects were noted. However, the basis for safety following repeated dosing of this compound comes from a separate clinical trial (M.B.A, Steven Dell, MD, George Lowry, MD, David G. Shulman, MD, and Francis J. Wapner, MD, unpublished data, 1998). In the safety study, ketotifen 0.025% ophthalmic solution was instilled 4 times daily for 6 weeks in healthy volunteers, including children as young as 3 years old, with normal ocular health. There were 495 subjects randomized into the trial, with 330 assigned to ketotifen and 165 assigned to placebo (data not presented). Results from this safety study did not identify any issues that would preclude the repeated use of ketotifen 0.025% solution. Taken together, it is concluded that ketotifen 0.025% is safe and well tolerated.

### Table 2. Subjects Reporting No Itching in Each Eye*

<table>
<thead>
<tr>
<th>Assessment Time After Challenge, min</th>
<th>Visit 3 (n = 89)</th>
<th>Visit 4 (n = 83)</th>
<th>Visit 5 (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>46 (51.7)</td>
<td>44 (53.0)</td>
<td>39 (54.2)</td>
</tr>
<tr>
<td>7</td>
<td>54 (60.7)</td>
<td>48 (57.8)</td>
<td>44 (61.1)</td>
</tr>
<tr>
<td>10</td>
<td>49 (55.1)</td>
<td>50 (60.2)</td>
<td>44 (61.1)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of ketotifen fumarate–treated eyes with no itching.

### Table 3. Effect of Ketotifen Fumarate on Conjunctival, Ciliary, and Episcleral Hyperemia in the Allergen Challenge Model*

<table>
<thead>
<tr>
<th>Assessment Time After Challenge, min</th>
<th>Visit 2 (n = 89)</th>
<th>Visit 3 (n = 89)</th>
<th>Visit 4 (n = 83)</th>
<th>Visit 5 (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival</td>
<td>0.03 (0.38)</td>
<td>−0.63 (0.86)†</td>
<td>−0.36 (0.71)†</td>
<td>−0.36 (0.60)†</td>
</tr>
<tr>
<td>Ciliary</td>
<td>0.04 (0.43)</td>
<td>−0.76 (0.95)†</td>
<td>−0.48 (0.66)†</td>
<td>−0.36 (0.71)†</td>
</tr>
<tr>
<td>Episcleral</td>
<td>0.03 (0.40)</td>
<td>−0.71 (0.85)†</td>
<td>−0.34 (0.66)†</td>
<td>−0.34 (0.62)†</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival</td>
<td>0.01 (0.33)</td>
<td>−0.53 (0.86)†</td>
<td>−0.19 (0.64)†</td>
<td>−0.20 (0.60)†</td>
</tr>
<tr>
<td>Ciliary</td>
<td>−0.01 (0.38)</td>
<td>−0.65 (0.98)†</td>
<td>−0.29 (0.67)†</td>
<td>−0.32 (0.63)†</td>
</tr>
<tr>
<td>Episcleral</td>
<td>0.01 (0.36)</td>
<td>−0.61 (0.91)†</td>
<td>−0.23 (0.64)†</td>
<td>−0.17 (0.65)§</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival</td>
<td>0.01 (0.35)</td>
<td>−0.54 (0.83)†</td>
<td>−0.17 (0.65)§</td>
<td>−0.17 (0.62)§</td>
</tr>
<tr>
<td>Ciliary</td>
<td>−0.01 (0.37)</td>
<td>−0.65 (0.94)†</td>
<td>−0.26 (0.65)†</td>
<td>−0.21 (0.65)†</td>
</tr>
<tr>
<td>Episcleral</td>
<td>0.01 (0.38)</td>
<td>−0.52 (0.86)†</td>
<td>−0.14 (0.66)§</td>
<td>−0.22 (0.68)†</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) difference between eyes. A negative difference indicates that the mean severity of injection was less in ketotifen-treated eyes compared with placebo-treated eyes.

†*P*<.001.

‡*P*<.01.

§*P*<.05.

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