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# Ketotifen Fumarate and Olopatadine Hydrochloride in the Treatment of Allergic Conjunctivitis: A Real-World Comparison of Efficacy and Ocular Comfort

**Michael Ganz, MD**
**Elizabeth Koll, CS-FNP**
**Jean Gausche, RN**
Ganz Allergy and Asthma Center
Racine, Wisconsin

**Paul Detjen, MD**
Kenilworth Medical Associates
Kenilworth, Illinois

**Nicholas Orfan, MD**
Hagerstown, Maryland

## ABSTRACT

This 3-week prospective, randomized, double-masked, parallel-group study compared ketotifen fumarate 0.025% ophthalmic solution and olopatadine hydrochloride 0.1% ophthalmic solution in 66 patients with seasonal allergic conjunctivitis. The drugs were instilled twice daily. Signs and symptoms were assessed on days 5 (visit 2) and 21 (visit 3). Other efficacy variables were the responder rate (patients with excellent or good global efficacy on days 5 and 21) and patient and investigator ratings of global efficacy. Comfort was evaluated immediately after instillation of the first drop and at each follow-up visit. The frequency of adverse events was the safety assessment. The responder rate was higher with ketotifen than with olopatadine on day 5 (72% vs 54% for patient assessment, 88% vs 55% for investigator assessment) and day 21 (91% vs 55%, 94% vs 42%). Global efficacy ratings were higher with ketotifen, and severity scores for hyperemia and itching were significantly lower. Both drugs elicited comparable comfort ratings. The most common adverse events were burning/stinging and headache.



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Address reprint requests to
Michael Ganz, MD
Ganz Allergy and Asthma Center
5802 Washington Avenue, Suite 103
Racine, WI 53406-4050

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## INTRODUCTION

As the most prevalent ocular allergy, seasonal allergic conjunctivitis affects approximately 25% of the US population.[1] The ocular component of hay fever, it usually coincides with peak pollen season[2] and characteristically manifests as ocular itching, redness, watery tearing, burning, foreign-body sensation, and eyelid edema.[3] Although seasonal allergic conjunctivitis is usually self-limiting and does not threaten vision, it can cause great discomfort.

Allergic conjunctivitis is triggered by airborne allergens binding IgE antibodies fixed to conjunctival mast cells, with resultant mast cell degranulation and release of chemical mediators.[4] These chemical mediators produce early- and late-phase responses.[5] The early, or acute, phase begins on allergen exposure and lasts 40 to 60 minutes. Histamine is the primary mediator of early-phase ocular symptoms, producing the hallmark itching and vasodilation. Two types of histamine receptors, $H_1$ and $H_2$, have been identified in the human conjunctiva.[6,7] Stimulation of $H_1$ receptors gives rise to itching; stimulation of $H_2$ receptors elicits redness.[6,7] The late phase occurs 2 to 24 hours after antigen exposure and results from the infiltration and activation of inflammatory eosinophils and macrophages.[5,8] During this phase, propagation of the allergic response promotes a resurgence of ocular symptoms.

Topical prescription medications have been the mainstay of therapy for allergic conjunctivitis,[9] attempting to provide both immediate relief of symptoms and long-term control. Dual- or multiaction drugs now combine the immediate relief obtained with topical antihistamines and the long-term control found with mast cell stabilizers.[10] Ketotifen fumarate has separate and distinct mechanisms of action—mast cell stabilization, histamine receptor antagonism, and eosinophil inhibition—that can lead to powerful and sustained inhibition of the allergic response.[11] Olopatadine is a widely used topical agent with antihistaminic and mast cell–stabilizing actions.[10,12-14]

This study compared the efficacy, tolerability, and safety of ketotifen and olopatadine administered to patients suffering from allergic conjunctivitis. The study design reflected real-life conditions.

## PATIENTS AND METHODS

### Patients

The study enrolled male and female patients at least 12 years of age and of any race, who were suffering from moderate (mild) to severe seasonal allergic conjunctivitis, defined by an ocular itching score of at least 2+ and characteristic symptoms (Table 1). Also required for entry were positive results of a skin test or radioallergosorbent test (RAST) within the past 24 months to at least one common allergen prevalent during the study period: ragweed pollen, molds (*Alternaria, Cladosporium, Fusarium, and Helminthosporium*), or other local weed pollens.

**Table 1. Scoring of Ocular Signs and Symptoms**

| Score | Signs and Symptoms |
|---|---|
| Conjunctival Hyperemia* | |
| 0 | Absent (vessels normal) |
| 1 | Mild (some vessels definitely injected above normal) |
| 2 | Moderate (diffusely red eye with individual vessels dilated but still not discernable) |
| 3 | Severe (intensely red eye with intensive dilation of conjunctival vessels) |
| Conjunctival Chemosis* | |
| 0 | Absent or visually not detectable |
| 1 | Visually evident, raised conjunctiva especially at limbal area |
| 2 | Ballooning of conjunctiva |
| Eyelid Swelling* | |
| 0 | Absent |
| 1 | Mild (lids are a little puffy) |
| 2 | Moderate (frank swelling of upper and lower lids) |
| 3 | Severe (eyelids are swollen shut) |
| Mucous Discharge | |
| 1 | Absent |
| 2 | Present |
| Itching* | |
| 0 | Absent |
| 1 | Intermittent tickle sensation involving more than just the inner corner of the eye |
| 2 | Mild continuous itch (can be localized) not requiring rubbing |
| 3 | Definite itch; you would like to be able to rub the eye |
| 4 | Incapacitating itch that would require significant eye rubbing |
| Tearing* | |
| 0 | Absent |
| 1 | Mild (eye feels slightly watery) |
| 2 | Moderate (occasional need to wipe eye) |
| 3 | Severe (tears rolling down cheeks) |

*.5-unit increments allowed.

The following exclusion criteria were in force: any ocular condition other than allergic conjunctivitis; history of ocular herpes, retinal detachment, diabetic retinopathy or any retinal disease, or the presence of any ocular condition that could have affected trial variables (particularly narrow-angle glaucoma; bacterial, viral, or follicular conjunctivitis; bacterial or viral ocular infections; iritis; preauricular lymphadenopathy; mucous discharge; excess lacrimation; or dry eye); concomitant use of topical medications with the potential to interfere with response to therapy or any condition requiring concurrent treatment with topical $H_1$ antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs, artificial tears, or lid scrubs; ocular surgery within 2 months of the study; treatment with investigational medications

or devices within the previous 4 weeks; and known hypersensitivity to any component of the study medications. To reflect a real-life setting, concomitant systemic and topical (nonocular) treatments (nasal drops/sprays/inhalers, oral inhalers) for allergic rhinitis or symptomatic asthma were allowed from the follow-up visit (days 5–8) to the end-of-study visit (days 21–25).

The trial was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board. All patients were paid for their participation.

## Design

This was a single-center, randomized, double-masked, parallel-dose evaluation of the efficacy, safety, and comfort of ketotifen fumarate 0.025% and olopatadine hydrochloride 0.1% as an active control. The study was conducted at an allergy/asthma center during the fall pollen season (August–October 2001) in the midwestern United States and involved three visits over 3 weeks.

### *Visit 1: Qualification, Baseline Assessment, and Treatment Assignment (Day 0)*

Eligible patients provided written informed consent and information on medical history, demographics, current diagnosis, and concomitant medications. An external eye examination by the physician evaluated the signs of allergic conjunctivitis (conjunctival hyperemia, conjunctival chemosis, eyelid swelling, and mucous discharge), and patients subjectively evaluated their symptoms (itching and tearing). Enrollment required an itching score of at least 2 (mild continuous itch not requiring eye rubbing; Table 1) and the bilateral presence of other signs/symptoms of seasonal allergic conjunctivitis. Following the patients' random assignment to treatment groups, a trained nurse coordinator instilled the first dose of medication, one drop in each eye, at the study center and 1 minute later queried patients about the ocular comfort of the medication. Patients rated ocular comfort on a five-point scale (Table 2). Patients were instructed to instill the medication twice daily (approximately 8 hours between doses) and to return to the physician's office between days 5 and 8 with the medication bottle.

**Table 2. Patient Assessment of Ocular Comfort/Tolerability**

| Grade* | Degree of Burning/Stinging |
|---|---|
| 0 | None |
| 1 | Mild (slightly perceptible) |
| 2 | Moderate (uncomfortable) |
| 3 | Severe (intense) |
| 4 | Very severe (extremely intense) |

*.5-unit increments allowed.

*Visit 2: Days 5 to 8*

One week later, medical and medication history was reviewed. Patients were questioned about compliance with the regimen and any adverse events since the last visit and used the same scale from visit 1 to grade overall ocular comfort. An external eye examination was performed to determine the degree of conjunctival hyperemia and the presence and intensity of conjunctival chemosis, eyelid swelling, and mucous discharge. Patients subjectively graded itching and tearing. Both the investigator and the patient provided an assessment of global efficacy relative to baseline (Table 3).

The bottle of masked medication was collected, and a new bottle was provided. Patients were instructed to return to the office in approximately 2 weeks (days 21–24).

**Table 3. Global Efficacy Ratings by Investigator* and Patients**

| | Rating | Description |
|---|---|---|
| 0 | Excellent | Complete or almost complete relief of ocular allergy symptoms |
| 1 | Good | Distinct relief |
| 2 | Fair | Some relief |
| 3 | Poor | No relief |
| 4 | Deterioration | Worsening |

*The investigator also used the same scale to rate signs of seasonal allergic conjunctivitis.

*Visit 3: End of Study, Days 21 to 24*

The evaluations performed during visit 2 were repeated. The bottle of masked medication was collected, and patients left the trial.

## Efficacy Assessments

The primary efficacy variable, the responder rate at visit 2, was determined by patients assessing the treatment in terms of symptomatic relief relative to baseline (see Table 3). A score of 0 or 1 (complete or distinct relief) defined a responder.

Secondary efficacy variables, assessed at both follow-up visits, were individual scores for signs and symptoms, patient and investigator assessments of global efficacy, and the responder rate (patient assessment at visit 3 and investigator assessment at visits 2 and 3).

## Tolerability and Safety Assessments

Monitoring of ocular comfort during the trial was intended to capture information under real-life conditions.

The primary safety variable was the frequency of ocular and nonocular adverse events, reported at visits 2 and 3. Adverse events were recorded throughout the study and were defined as any clinically relevant worsening from the baseline examination.

## Statistical Analyses

Responder rates and ratings of global efficacy, signs, symptoms, and comfort were compared between groups with an analysis of variance and mixed-model procedures (SAS Institute, Cary, NC). All tests were two sided; a *P* value less than or equal to .05 was considered statistically significant. For validity, the right and left eyes were examined separately, in anticipation of similar outcomes. All reported events, serious events, and discontinuations due to adverse events were summarized by number and percentage.

# RESULTS

All 66 screened individuals qualified for entry, were randomly assigned to treatment with either ketotifen (n=32) or olopatadine (n=34), and were evaluated for efficacy and safety. The entire ketotifen group completed the trial, as did 31 patients in the olopatadine group. One olopatadine-treated patient was discontinued at visit 1 owing to significant burning and stinging, and 2 additional patients in this group were lost to follow-up at visit 3.

## Baseline Characteristics

No statistical differences in demographics or baseline characteristics were found between the two groups (Table 4). The average age of the patients was 36.2 years, approximately 75% of each group were women, and 93.9% were white, reflecting the Wisconsin population. The most common iris colors were brown (33.3%), blue (3.3%), and hazel (19.7%). Initial and follow-up medical histories showed no between-group differences in concomitant therapy.

**Table 4. Baseline Characteristics**

| | No. (%) of Patients | |
|---|---|---|
| | **Ketotifen (n=32)** | **Olopatadine (n=34)** |
| Sex | | |
| Female | 24 (75) | 25 (73.5) |
| Male | 8 (25) | 9 (26.5) |
| Age, y* | 37.47±16.8 | 35.2±14.4 |
| Race | | |
| White | 28 (87.5) | 34 (100) |
| Other | 4 (12.5) | 0 (0) |
| History of ocular allergy | | |
| Yes | 8 (25) | 6 (17.7) |
| No | 24 (75) | 28 (82.3) |
| Positive skin test | | |
| Yes | 28 (87.5) | 33 (97.1) |
| No | 4 (12.5) | 1 (2.9) |

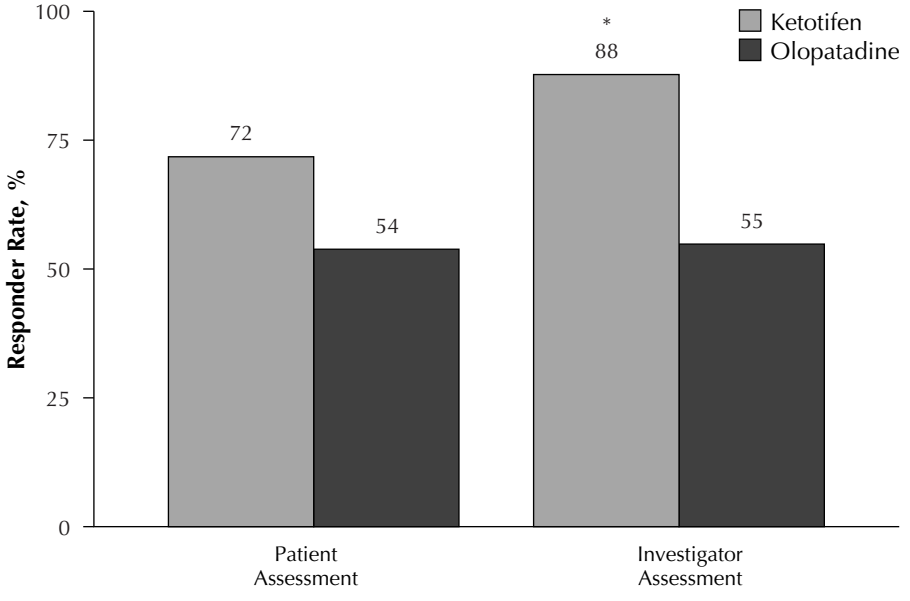
*Mean ± SD.

## Efficacy

### *Responder Rate*

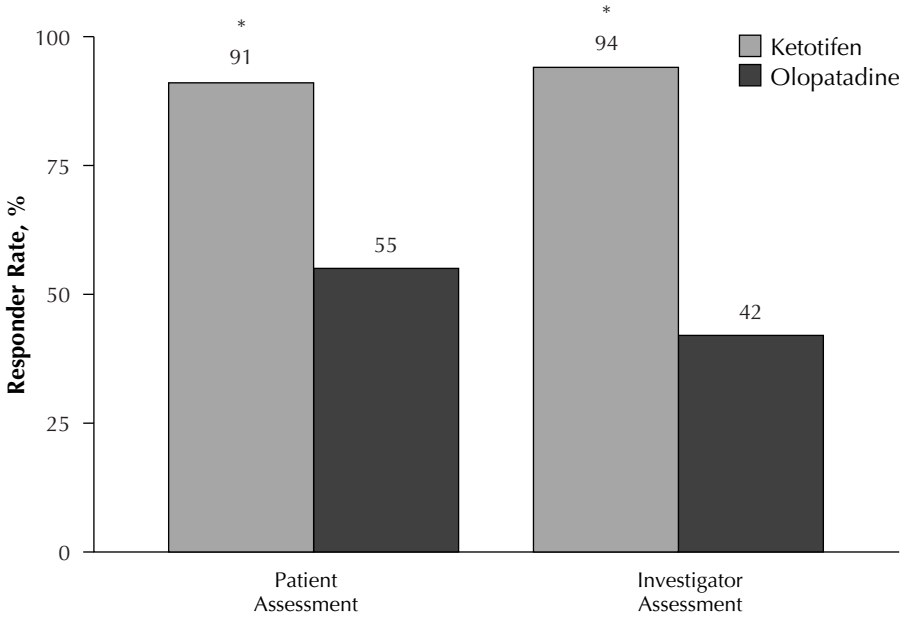
At the first (Fig 1) and second (Fig 2) follow-up visits, more patients responded to treatment with ketotifen than to olopatadine, according to both patient and investigator assessments. The difference between groups was statistically significant for the investigator evaluation at visit 2 ($P<.0001$) and for the patient ($P=.0001$) and investigator ($P<.0001$) evaluations at visit 3.

**Fig 1. Responder rate (excellent or good global efficacy) at days 5 to 8 (visit 2) after treatment with ketotifen fumarate or olopatadine hydrochloride.**




*$P<.0001$.

**Fig 2. Responder rate (excellent or good global efficacy) at days 21 to 24 (visit 3) after treatment with ketotifen fumarate or olopatadine hydrochloride.**




*$P \leq .0001$.

## *Global Efficacy*

At each follow-up visit, patients and investigators found ketotifen superior to olopatadine in relieving the signs and symptoms of allergic conjunctivitis (Table 5). For each treatment group, mean global efficacy scores were compared between visit 2 (day 5) and visit 3 (day 21). Within the groups, no statistically significant differences emerged between visits, although ketotifen-treated patients showed a numeric improvement from visit 2 to visit 3.

**Table 5. Mean Global Efficacy Based on Patient and Investigator Assessments***

| | Day | Ketotifen | Olopatadine | *P* Value |
|---|---|---|---|---|
| Patient | 5 | .91 | 1.36 | .03 |
| | 21 | .72 | 1.49 | .0005 |
| Investigator | 5 | .66 | 1.36 | .001 |
| | 21 | .56 | 1.53 | <.0001 |

*Rated on a 0–4 scale; see Table 3.

## *Ocular Signs and Symptoms*

Individual and total sign and symptom scores were compared between groups at baseline and at the two follow-up visits (Tables 6 and 7). Conjunctival chemosis, eyelid swelling, and mucous discharge were absent in the majority of patients (only 2 participants presented with conjunctival chemosis; 1 each had eyelid swelling and mucous discharge), reflecting a real-world observation in this practice. For this reason, these signs were not compared individually but were included in the total scores. The major allergic manifestation was ocular itching. At baseline, no significant differences were found between the treatments for individual or total sign and symptom scores. At both follow-up visits, the ketotifen group had significantly lower scores for conjunctival hyperemia and itching; scores for tearing did not differ between treatments.

**Table 6. Individual Sign and Symptom Scores, by Treatment**

| Sign/Symptom | Day | Eye | Ketotifen | Olopatadine | *P* Value |
|---|---|---|---|---|---|
| Conjunctival hyperemia | 0 | Right | .322±.564 | .177±.424 | .196 |
| | | Left | .328±.562 | .206±.566 | .296 |
| | 5 | Right | .016±.088 | .227±.397 | .048 |
| | | Left | .016±.088 | .273±.435 | .032 |
| | 21 | Right | .016±.088 | .339±.651 | .003 |
| | | Left | .016±.088 | .387±.715 | .003 |
| Itching | 0 | Right | 2.344±.410 | 2.353±.399 | .951 |
| | | Left | 2.359±.406 | 2.353±.399 | .966 |
| | 5 | Right | .234±.458 | .652±.897 | .007 |
| | | Left | .219±.457 | .621±.884 | .008 |
| | 21 | Right | .156±.296 | .823±.909 | <.0001 |
| | | Left | .156±.296 | .839±.916 | <.0001 |
| Tearing | 0 | Right | .594±.827 | .676±.976 | .595 |
| | | Left | .547±.846 | .662±.983 | .463 |
| | 5 | Right | .156±.390 | .227±.588 | .652 |
| | | Left | .125±.381 | .212±.587 | .583 |
| | 21 | Right | .047±.148 | .177±.439 | .409 |
| | | Left | .032±.148 | .177±.439 | .356 |

Changes in the individual and total scores were also compared between visits for each group. Between baseline and visit 2 (days 5–8), treatment with ketotifen significantly decreased conjunctival hyperemia, itching, and tearing, along with total signs and symptoms; treatment with olopatadine significantly decreased itching, tearing, and total symptom scores. Between days 5 and 21, ketotifen maintained or further reduced, though nonsignificantly, conjunctival hyperemia, itching, and tearing, as well as total sign and symptom scores. Between the same timepoints, there was a slight but not significant loss of efficacy with olopatadine for all outcome variables, except tearing.

**Table 7. Total Sign and Symptom Scores, by Treatment**

| | Day | Eye | Ketotifen | Olopatadine | *P* Value |
|---|---|---|---|---|---|
| Signs | 0 | Right | .322±.564 | .250±.511 | .658 |
| | | Left | .328±.562 | .279±.630 | .752 |
| | 5 | Right | .016±.088 | .364±.616 | .015 |
| | | Left | .016±.088 | .409±.631 | .013 |
| | 21 | Right | .016±.088 | .532±1.008 | .0004 |
| | | Left | .016±.088 | .613±.116 | .0002 |
| Symptoms | 0 | Right | 2.938±.948 | 3.029±1.148 | .691 |
| | | Left | 2.906±.963 | 3.015±1.151 | .647 |
| | 5 | Right | .391±.632 | .879±1.046 | .036 |
| | | Left | .344±.606 | .833±1.157 | .041 |
| | 21 | Right | .203±.356 | 1.000±1.190 | .001 |
| | | Left | .188±.354 | 1.016±1.194 | .0009 |
| Total signs and symptoms | 0 | Right | 3.250±1.615 | 3.279±1.846 | .926 |
| | | Left | 3.234±1.622 | 3.294±1.919 | .857 |
| | 5 | Right | .406±.228 | 1.243±.225 | .010 |
| | | Left | .359±.238 | 1.240±.235 | .009 |
| | 21 | Right | .219±.228 | 1.532±.232 | <.0001 |
| | | Left | .203±.238 | .169±.242 | <.0001 |

### *Ocular Comfort*

At all visits, ketotifen and olopatadine were rated between 0 (comfortable, no sensation) and 1 (mild, slightly perceptible sensation). No significant differences were found between treatments.

## Safety

One serious treatment-related adverse event occurred. One patient in the olopatadine group experienced severe discomfort in the eyes on instillation at visit 1 and asked to be discontinued from the trial. Other adverse events were mild to moderate. The most common ocular adverse events were burning and stinging, reported by two patients using ketotifen and three patients using olopatadine. Headache, the most common systemic adverse event, was cited by one ketotifen-treated patient and two olopatadine-treated patients.

# DISCUSSION

In this 3-week real-world environmental study, ketotifen was superior to olopatadine in relieving and controlling the signs and symptoms of seasonal allergic conjunctivitis. Responder rates and measurements of global efficacy, assessed by patients and investigators, were significantly higher for ketotifen. Individual scores demonstrated that ketotifen reduced ocular signs and symptoms and maintained the reduction to a greater extent than did olopatadine. No significant dif-

ferences in ocular comfort and tolerability were found between the groups. Safety, as measured by adverse events, was also similar with both treatments.

Topical treatments for ocular allergies have advantages over systemic products that include a more rapid onset of action (within 3 minutes) and minimal systemic adverse effects.[15] Newer dual-acting[10,14,15] and multiple-acting agents[11] offer antihistaminic properties for immediate relief and additional effects on the mediators of the late-phase reaction. The greater efficacy of ketotifen demonstrated in this trial may be the result of its multiple and distinct modes of action on the allergic cascade. Ketotifen blocks both $H_1$ and $H_2$ receptors more effectively than does olopatadine.[15] The higher receptor affinity of ketotifen may contribute to its less-frequent dosage schedule compared with that of olopatadine. (The recommended dose of ketotifen is one drop twice daily in the affected eye[s] every 8 to 12 hours[16]; the recommended dose of olopatadine is one drop in each affected eye twice daily at 6- to 8-hour intervals.[17]) Studies with human mast cells have shown ketotifen to be more effective than olopatadine in inhibiting degranulation and the release of histamine (the mean inhibitory concentration of ketotifen is approximately 100-fold less than that of olopatadine).[13] Although in vitro data suggest a biphasic effect of ketotifen on mast cells (inhibition of histamine release at lower concentrations and spontaneous release at higher concentrations), this effect has not been noted in vivo with either the 0.025% or 0.05% formulation.[18-20]

The present results contrast with those of a comparison of ketotifen and olopatadine that used the conjunctival allergen challenge model[21] in 32 patients who were pretreated with one of the drugs in each eye.[18] Immediately following instillation, the comfort level of the drop was rated on a nine-point scale (0=comfortable, 8=uncomfortable). Both drugs elicited similar scores (between 1 and 2), although those for olopatadine were statistically lower than those for ketotifen. Twelve hours after drug instillation, participants were challenged with antigen, and itching was assessed 3, 5, and 10 minutes later. Both drugs similarly reduced itching scores (between 1 and 2 units, mean efficacy score) and were clinically effective in decreasing itching (mean efficacy reduction more than 1 unit from placebo). The olopatadine score, however, was statistically, but not clinically, better than the ketotifen score.

These disparate results are likely to be a function of the study design: the conjunctival allergen challenge model[18] versus an environmental model. Although the allergen challenge model is the gold standard for evaluating various aspects of the ocular immune response and the inhibitory effects of drugs,[22] it does not provide information on long-term efficacy or tolerability. The environmental analysis in the present study was intended to compare the two agents in a real-life clinical setting with true allergen exposure during a typical allergy season. A shortcoming of environmental studies has been the large placebo effect arising from the washing away of allergens by placebo drops.[22] An active control in this study ensured that any antigen washout would affect both groups similarly. The previous allergen study[18] compared a single dose of two drugs at the same time in the same individual and was able to detect small differences in the efficacy and comfort/tolerability of ketotifen and olopatadine. In the current 3-week environmental study, the efficacy comparison under actual use demonstrated the superiority of ketotifen to olopatadine and found no differences in comfort or tolerability between the drugs.

The two other comparisons[19,20] of ketotifen and olopatadine examined a 0.05% formulation of ketotifen, not currently marketed in the United States, and were not considered relevant to the current study.

## CONCLUSIONS

In a 3-week study under actual-use conditions during fall allergy season, ketotifen fumarate 0.025% ophthalmic solution was superior to olopatadine hydrochloride 0.1% ophthalmic solution in relieving the signs and symptoms of allergic conjunctivitis. No differences in comfort, tolerability, or safety were noted between groups over the course of the study. The superior efficacy and sustained inhibition of the allergic response make ketotifen an ideal treatment option for allergic conjunctivitis.

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