Efficacy and comfort of olopatadine versus ketotifen ophthalmic solutions: a double-masked, environmental study of patient preference

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Key words: Comfort – Ketotifen – Ocular allergy – Olopatadine – Patient preference

Background: Ocular allergies cause itching, redness, chemosis, tearing, and swelling of the eyelids in sensitized individuals. The options available for treatment of ocular allergy include olopatadine 0.1% (Opatanol; Patanol [US]*) and ketotifen 0.025% (Zaditen; Zaditor [US]†). Patient preference for an eye drop can often be a primary factor in determining the level of compliance and satisfaction with any given therapy.

Objective: This study sought patient perspective on eye drop efficacy in controlling signs and symptoms of allergic conjunctivitis and eye drop comfort. Also evaluated were the factors considered by patients when making decisions of preference.

Methods: One hundred patients with previous history and current symptoms of seasonal or perennial allergic conjunctivitis were enrolled at two centers (Athens, Greece, N = 50; Padova, Italy, N = 50) for this two visit, double-masked study. Qualified patients received two masked bottles of medication (one olopatadine, one ketotifen) and were asked to use both medications as needed over the course of four weeks, but not to exceed usage of two drops of medication per eye per day. At the second visit, patients answered five questions comparing the two masked medications in terms of preference, drop comfort, and efficacy in treatment of signs and symptoms. Patients also defined the factors upon which they based these decisions.

Results: A significantly greater percentage of patients (81%) selected olopatadine when asked which medication they preferred; which they found more comfortable; which they found more efficacious in reducing symptoms of allergy; and which they would select if visiting the doctor's office (P < 0.0001). Seventy-six percent (76%) of patients considered both efficacy and comfort when making their preference decisions (P < 0.0001). No adverse events were volunteered or elicited.

Conclusion: In this study, patients preferred to use the anti-allergy eye drop olopatadine over ketotifen after using both drops and evaluating relative efficacy and comfort during the course of four weeks. A significantly greater percentage of the patients preferred to use olopatadine during the study period, found it more efficacious and comfortable, and would select olopatadine if visiting their doctor's office during allergy season.

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* Opatanol and Patanol are registered trade names of Alcon Laboratories, Inc, Fort Worth, TX, USA
† Zaditen and Zaditor are registered trade names of Novartis Pharmaceuticals, East Hanover, NJ, USA
Introduction

Ocular allergies occur when sensitized individuals are exposed to specific airborne allergens. An allergen, once it has reached the eye, binds to IgE on conjunctival mast cells triggering a cascade of reactions resulting in the release of histamine and other allergic and inflammatory mediators from the mast cell. Histamine is the primary mediator released, and the only mediator that has been shown to cause the entire spectrum of signs and symptoms of ocular allergy (itching, redness, chemosis, lid swelling, and tearing). Itching is the hallmark symptom of ocular allergy, and can impact patients’ ability to go about daily functions, while the redness and lid swelling of allergy are the predominant signs of allergy and can cause concern about appearance, as well as discomfort.

The incidence of allergy (rhinoconjunctivitis) in Europe has been assessed by various recent epidemiological studies to be present in 10 to over 22% of the general population in several European countries. The International Study of Asthma and Allergies in Childhood (ISAAC) revealed a maximum of 54.4% of 13–14 year olds at 155 centers having had hay fever, however this study also indicated that the prevalence of allergic rhinoconjunctivitis varies widely amongst age groups and geographical areas. Centers having the highest prevalence were scattered throughout the world with no distinct geographical pattern. In addition, it has been noted that the incidence of allergy is rising and that urban/industrialized areas with elevated levels of air pollutants may lead to increased susceptibility toward allergens.

Factors that may aid in improving the treatment of ocular allergy in Europe include recognizing the patient population in need of treatment, and assigning the appropriate treatment for each individual patient’s needs. The majority of anti-allergy medication used in many European countries is either systemic or consists of older-generation mast cell stabilizers (cromoglycates). Recently, newer options for anti-allergy eye drops have also become available in Europe. Olopatadine hydrochloride 0.1% (Opatanol; Patanol (US)) is indicated for the treatment of signs and symptoms of seasonal allergic conjunctivitis (itching, redness, chemosis, lid swelling and tearing). Ketotifen fumarate 0.025% (Zaditen; Zaditor (US)), while the indication does vary by market, is indicated in Italy and Greece for the signs and symptoms of perennial allergic conjunctivitis, including eyes or lids suffering from itching, watery discharge, redness, and swelling.

Olopatadine is an H1 receptor specific antihistamine and mast cell stabilizer that inhibits the immediate hypersensitivity reaction. Olopatadine was developed specifically as an ophthalmic agent for use in the human conjunctiva, and it has demonstrated the ability to stabilize human conjunctival mast cells both in vitro and in vivo. In clinical trials, olopatadine has demonstrated efficacy for at least 12 hours in the Conjunctival Allergen Challenge (CAC) Model.

Ketotifen, originally a molecule used in asthma treatment, works via a mechanism with antihistaminic and mast cell stabilizing effects. It has shown a duration of action up to 12 hours in reducing ocular itching in the CAC clinical model and has a favorable safety and tolerability profile.

The gathering of patient perception data will be important in determining therapy options patients are more satisfied with, therefore increasing the ability of the practitioner to select the primary therapy with greater chances of yielding successful treatment. Novel mechanisms of action can be important advancements, however, the actual success of a therapy can hinge on the selection or recommendation by the medical practitioner. The compliance and satisfaction of patients can be valuable information to the practitioner in making this important decision.

This study sought the patient’s perspective on eye-drop efficacy in controlling signs and symptoms of allergic conjunctivitis and comfort, while also taking into account what factors patients considered when making their decisions of preference. The efficacy of ketotifen and olopatadine has been compared in controlled studies, and the comfort of olopatadine and ketotifen has been compared previously. The current study compares both efficacy and comfort of olopatadine and ketotifen in an environmental model that allows patients to determine which medication is more effective and comfortable during daily airborne allergen exposure. In this study we use this type of evaluation to determine whether one of two therapy options is significantly preferred by patients for use throughout the allergy season.

Methods

This was a multi-center, double-masked, environmental patient preference clinical trial. The study protocol and informed consent were reviewed and approved by an ethics committee. The study consisted of two visits conducted in the fall of 2003, during which time airborne allergens including ragweed, goosefoot, Alternaria and Cladosporium are present. One hundred patients with previous history and presenting at Visit 1 with signs and symptoms (hyperemia and ocular itching) of seasonal or perennial allergic conjunctivitis were enrolled at two centers (Athens, Greece, N = 50; Padova, Italy, N = 50). A sample size of 80 gave a 95% confidence level to detect a statistically significant difference of 0.05% assuming a margin of error of 5% and a response distribution of 50%.

Visit 1

Demographic data were recorded, and each qualified patient was dispensed a diary in which to record medication usage and efficacy, and two masked bottles of medication (1 bottle of olopatadine 0.1% [Opatanol], 1 bottle of ketotifen 0.025% [Zaditen]). In this real-world scenario, patients were instructed to use both medications as needed over the course of four weeks, but not to exceed usage of two drops of medication per eye per day. Patients were required to use both bottles during the study but were allowed to use their own discretion to determine the number of times required to use each medication to determine preference. Patients were permitted to use study medication concomitantly with their regular medical therapies.

Visit 2

After four weeks of recording eye drop bottle usage daily, patients returned for visit 2. Medication was collected and subjects were asked to fill out a questionnaire asking them to compare the two masked medications in terms of comfort and efficacy in treatment of their symptoms of itching, redness, and lid swelling. Patients were asked the questions set out in Table 1. Similar comfort questions have been used in previous comparisons, however the other questions are novel to this environmental study design.

No objective investigator gradings of signs or symptoms were conducted at this visit. This eliminated the possibility of investigator evaluations influencing patient perception of efficacy.

Statistical Analyses

Percentages were calculated by treatment according to patient answers to each of the question; if a patient selected A and B in answer to questions 1–4, this was considered a ‘no preference’ vote. P values based on the difference in the number of times subjects chose one treatment versus the other were calculated using the Sign Test. A P value < 0.05 was considered statistically significant.

Table 1. Questionnaire given to patients to complete at visit 2, after four weeks of daily eye-drop usage

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which medication did you prefer to use more often?</td>
<td>A or B</td>
</tr>
<tr>
<td>Which medication worked better at relieving your eye allergy signs and symptoms (examples: itchiness, redness, lid swelling)?</td>
<td>A or B</td>
</tr>
<tr>
<td>Which medication was more comfortable?</td>
<td>A or B</td>
</tr>
<tr>
<td>If you visited your doctor’s office during allergy season, which bottle would you ask for?</td>
<td>A or B</td>
</tr>
<tr>
<td>How did you determine your preference?</td>
<td>Efficacy, Comfort Both</td>
</tr>
</tbody>
</table>

Table 2. Demographic data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Italy</th>
<th>Greece</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
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<td>14.30</td>
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<tr>
<td>Race:</td>
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<td></td>
</tr>
<tr>
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<td>98.00</td>
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<tr>
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<td>2.00</td>
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<td>Missing data</td>
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<td>0.00</td>
</tr>
<tr>
<td>Eye color:</td>
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<td></td>
</tr>
<tr>
<td>Blue</td>
<td>13</td>
<td>26.00</td>
</tr>
<tr>
<td>Brown</td>
<td>18</td>
<td>36.00</td>
</tr>
<tr>
<td>Green</td>
<td>8</td>
<td>16.00</td>
</tr>
<tr>
<td>Hazel</td>
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<td>16.00</td>
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<tr>
<td>Grey</td>
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<td>0.00</td>
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<tr>
<td>Sex:</td>
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</tr>
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<td>50.00</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>50.00</td>
</tr>
</tbody>
</table>

SD = Standard deviation
Results

All patients \((N = 100)\) completed the study as planned and answered the patient preference questionnaires at the conclusion of 4 weeks usage of masked study medications. Patients returned a daily diary in which they had tracked compliance by recording the number of drops used from each bottle each day. All subjects, as instructed (see Methods), used both bottles of eyedrops during the 4-week study period. Demographic data for both sites is presented in Table 2. No adverse events were volunteered or elicited.

Patients reported a significant preference for using olopatadine, with 81% indicating this preference, 17% preferring ketotifen, and 2% indicating no preference (Figure 1) \((P < 0.0001)\).

The following two questions separated this overall preference rating into distinct ratings of efficacy and comfort. When asked which medication provided better relief of signs and symptoms of ocular allergy, such as itching, redness, and lid swelling, 81% of patients chose olopatadine, 19% selected ketotifen, and zero indicated no preference (Figure 2) \((P < 0.0001)\).

A significant percentage of patients selected olopatadine as more comfortable (81%) compared to ketotifen (18%) \((P < 0.0001)\); 1% indicated no preference (Figure 3).

In response to the fourth question regarding the drop patients would request if visiting the doctor’s office during allergy season, 81% would request olopatadine, 18% ketotifen, and 1% had no preference (Figure 4). The difference between olopatadine and ketotifen was significant \((P < 0.0001)\).
Figure 3. Patient (N = 100) responses when asked, ‘Which medication was more comfortable?’ A significantly greater percentage of patients selected olopatadine as compared to ketotifen (P < 0.0001)

Figure 4. Patient (N = 100) responses when asked, ‘If you visited your eye doctor’s office during allergy season, which bottle would you ask for?’ A significantly greater percentage of patients selected olopatadine, significantly greater than ketotifen (P < 0.0001)

Figure 5. Patients (N = 100) were asked ‘How did you determine your preference?’ The group considering both efficacy and comfort was significantly larger than those basing their decision on efficacy alone or comfort alone (P < 0.0001)
The selection made in the previous question was based on patients’ evaluation of both efficacy and comfort in 76% of the patients. This group of patients was significantly greater than either those basing their evaluation only on efficacy (18%), or only on comfort (6%) (Figure 5) \( P < 0.0001 \).

**Discussion**

This study was conducted to determine the patient preference between two topical anti-allergy eye drops after four weeks of treatment. These two eyedrops have previously been compared with regard to their ability to manage signs and symptoms. However, the goal of this study differed in that it was intended to study patient preference and comfort. Objective evaluation of eye-drop efficacy, while important, is not the only factor in determining the optimal therapy for patient care. The comfort, convenience, and patient perception of efficacy are also defining factors in selection. In this study, most patients indicated that they evaluated both efficacy and comfort in deciding between two treatments.

The response of patients in this double-masked study in which both ketotifen and olopatadine were used indicated that a significantly greater percentage (81%; \( P < 0.0001 \)) of patients preferred to use olopatadine. Seventy-six percent of patients indicated their preference ratings were based on both comfort and efficacy. The results of individual questions on efficacy (Question 2) and comfort (Question 3) confirmed this, with the same percentage of patients (81%) indicating a preference for olopatadine in answer to each question.

The efficacy of olopatadine and ketotifen has been compared in previous conjunctival allergen challenge studies. In one study evaluating itching, eyes were challenged with allergen 12 hours after instillation of medication, and itching was evaluated by subjects on a standardized 0–4 scale. Significantly superior management of itching was evident with olopatadine use \( (N = 32; P < 0.05) \). In a second study evaluating all signs and symptoms of allergy, the percent of patients for whom itching and redness was sufficiently controlled was significantly greater for those administering olopatadine as compared to ketotifen \( (N = 80; P < 0.05) \). Of note is that the above-referenced study used a more concentrated solution (0.05%) of ketotifen than that which is currently available in the US and Europe. However, olopatadine 0.1% provided significantly greater efficacy in this scenario. The difference in efficacy observed in these studies is also consistent with the patient preference observed in the current study.

Previous study of the relative comfort of olopatadine and ketotifen has also yielded results consistent with those of the current study. In a contralaterally controlled study comparing the relative efficacy and clinical performance of olopatadine and ketotifen, olopatadine-treated eyes were rated as significantly more comfortable than those treated with ketotifen \( (P < 0.05) \). A patient choice (i.e. forced choice) study resulted in 100% of patients \( (N = 80) \) selecting olopatadine as a more comfortable drop than ketotifen, after receiving a drop of olopatadine in one eye and a drop of ketotifen in the other eye. One study has noted comparable comfort ratings between the two agents. It should be noted that the above-referenced study used parallel-group design, and patients received only one of the two drops throughout the study. Conversely, in the former two studies, contralateral dosing was used so that each patient experienced both study medications and could accurately assess their relative comfort.

One factor contributing to the comfort of olopatadine at the clinical level may be the compound’s behavior at the molecular level. A laboratory \((in vitro)\) study examined the interactions of several anti-allergy molecules with model and natural membranes (human conjunctival mast cells and epithelial cells, erythrocytes) to evaluate whether the therapeutic compounds had any detrimental effects on the function of these membranes. The results indicated that most of the therapeutic molecules tested \((i.e.\ desloratadine, clemastine, azelastine, ketotifen, diphenhydramine, pyrilamine, emedastine, and epinastine) had direct detrimental effects causing disruption to cell membranes. In this same model olopatadine had minimal perturbation of these membranes. This is one property of olopatadine which is believed to contribute to its comfort profile.

**Conclusion**

In this study, patients preferred to use the anti-allergy eye drop olopatadine over ketotifen, after using both drops and evaluating their relative efficacy and comfort over a four week treatment period. A significantly greater portion of the patients preferred to use olopatadine, found it more efficacious and comfortable, and would select to use olopatadine if visiting their doctor’s office during allergy season. These results in an environmental model confirm the results of previous conjunctival allergen challenge (CAC) studies evaluating efficacy and patient choice models evaluating comfort. This reinforces olopatadine’s performance in a variety of settings and implies that the results of prior drug evaluation in the CAC model are applicable in actual clinical practice.
Acknowledgement

This study was supported by an unrestricted grant from Alcon Laboratories, Inc, Fort Worth, Texas.

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http://www.cmrojournal.com
Paper CMRO-2627, Accepted for publication: 00 May 2004
Published Online: 11 June 2004
doi:10.1185/030079904125004321