Efficacy and Safety of Ketotifen Eye Drops as Adjunctive Therapy to Mometasone Nasal Spray in Subjects with Seasonal Allergic Rhinoconjunctivitis

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Abstract

Objective: To compare the efficacy and safety of ketotifen 0.025% ophthalmic solution (one drop/eye) with placebo as adjunctive therapy to mometasone nasal spray (50 μg/spray, two puffs/nostril) in subjects with seasonal allergic rhinoconjunctivitis (SARC).

Study design: Single-centre, randomised, double-masked, two-treatment, two-period crossover study.

Setting: 8-hour allergen challenge in the Vienna Challenge Chamber.

Study participants: Subjects were ≥18 years old, had a ≥2-year history of SARC, and were sufficiently responsive to allergen challenge.

Interventions: During each challenge, subjects received a single dose of mometasone + ketotifen or mometasone + placebo.

Main outcome measures and results: 47 subjects were randomised, and 44 completed both treatment sequences. Efficacy was based on mean area under the curve (AUC) values for symptom relief scores over time, with the primary variable being the AUC 4–6 hours postdose (AUC<sub>4–6</sub>) for relief of ocular itching. Between-treatment differences were assessed using analysis of variance. While improvement in ocular itching (AUC<sub>4–6</sub>) was observed with both treatments, improvement was significantly (p = 0.014) better with mometasone + ketotifen versus mometasone + placebo, as was improvement based on AUC<sub>0–6</sub> (p = 0.009) and AUC<sub>0–2</sub> (p = 0.006). Similar trends (in favour of mometasone + ketotifen) were observed for improvements in ocular redness, running nose, sneezing and ocular/nasal composite scores (p ≤ 0.05). None of the safety findings (slit-lamp biomicroscopy, vital signs, adverse events) were clinically significant. One subject discontinued treatment due to mild pharyngitis.

Conclusion: Ketotifen eye drops adjunctive to mometasone nasal spray provided greater relief of both ocular and nasal signs and symptoms than mometasone alone in subjects with SARC.
Seasonal allergic rhinoconjunctivitis (SARC) is a common medical condition caused by hypersensitivity to specific airborne allergens, namely pollens. It has been estimated that SARC affects as many as 10% of the European population, and there are reports suggesting a substantial increase in the prevalence of allergic conditions over the past few decades. Typical clinical manifestations include ocular symptoms of redness, pruritus, lacrimation and eyelid oedema accompanied by nasal pruritus, sneezing, rhinorrhea and congestion.

The immunopathogenesis of ocular allergy is complex and results from a series of multiple molecular and cellular interactions. The vast majority of signs and symptoms of allergic rhinoconjunctivitis are initiated by allergen-IgE antibody-mast cell interaction, causing degranulation of the mast cell. This process leads to release of mast cell mediators (e.g. histamine, leukotrienes, prostaglandins, platelet-activating factor) that stimulate nerve endings, induce vasodilation, increase vascular permeability, and activate leucocyte chemotaxis.

While the signs and symptoms of allergic rhinitis are generally mild to moderate in intensity, some subjects experience a great deal of discomfort that significantly reduces their quality of life. The current approach for treating SARC involves the identification and subsequent avoidance of the offending allergen(s) coupled with pharmacological inhibition of inflammatory mediators. Immuno-modulation (i.e. allergen desensitisation therapy) may also be used, although risk of anaphylaxis and other adverse effects related to immunotherapy may limit its use.

Currently, four different classes of medications are available to alleviate the signs and symptoms of allergic rhinoconjunctivitis: antihistamines (histamine H1-receptor antagonists), mast cell stabilisers, corticosteroids and NSAIDs. Antihistamines are often used as first-line therapy, particularly ophthalmic and nasal formulations that directly target the involved site(s) to provide rapid symptom relief without significant systemic side effects. However, since histamine is not the only factor involved in the pathogenesis of the disease, these compounds do not completely alleviate all of the signs and symptoms associated with the condition. Hence, subjects with allergic conjunctivitis and rhinitis often require more than one medication to obtain optimal relief. Drugs acting on different aspects of the allergic response are often used in combination to treat these conditions.

Ketotifen, a topical therapy for allergic conjunctivitis, is a benzocycloheptathiophene derivative that targets multiple facets of the allergic response. In addition to being a potent H1-receptor antagonist, ketotifen inhibits the release of inflammatory mediators from mast cells. It also reduces the chemotaxis, activation and degranulation of eosinophils. Ketotifen eye drops have a rapid onset of action (within minutes) and long duration of effect (8–12 hours), allowing for almost immediate symptom relief coupled with the convenience of twice-daily dosing.

To date, no published studies have evaluated ketotifen eye drops as adjunctive therapy to other antiallergy medications for controlling the signs and symptoms associated with SARC. This trial was designed to evaluate the efficacy and safety of ketotifen 0.025% eye drops (Zaditen®/Zaditor™, Novartis Ophthalmics, Bühlach, Switzerland) as adjunctive therapy to mometasone nasal spray (Nasonex®, ESSEX Pharma GmbH, Munich, Germany), a synthetic corticosteroid approved for the treatment of seasonal and perennial allergic rhinitis, in subjects with SARC under controlled conditions of allergen challenge.

Subjects and Methods

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from each subject prior to the initiation of any study-related procedures.

1 The use of tradenames is for product identification purposes only and does not imply endorsement.
Study Design and Procedures

This was a prospective, single-centre, double-masked, randomised (1:1), placebo-controlled, two-treatment, two-period crossover, allergen challenge trial conducted under standardised conditions in the Vienna Challenge Chamber (VCC). When used during the allergy-free season, the VCC offers the best opportunity to monitor the course of drug action on allergic response under controlled conditions in subjects who are provoked with an offending allergen at concentrations typically encountered during allergy season. This model has been extensively used in the evaluation of other antiallergic agents in subjects with allergic rhinitis and/or conjunctivitis.\(^{[17-22]}\)

The trial involved five study visits: visit 1 (screening, days –21 to –3); visit 2 (start of period 1, day –2); visit 3 (allergen challenge for period 1, day 0); visit 4 (start of period 2, day 12); and visit 5 (allergen challenge for period 2, day 14, study termination). Visits 3 and 4 were separated by at least 12 days to allow for adequate washout of allergen and drug (figure 1).

At visit 1, subjects were assigned a unique screening number in ascending order as they qualified for study participation.

At visits 2 and 4, subjects received mometasone (50 µg/metered spray, two puffs/nostril) in the morning at the site. Subjects were then dispensed one open-label bottle of mometasone and instructed to administer two puffs per nostril one morning before visits 3 and 5. At visit 3, subjects were randomised to one of two treatment sequences to receive either (i) ketotifen + mometasone at visit 3 and placebo + mometasone at visit 5 (sequence 1); or (ii) placebo + mometasone at visit 3 and ketotifen + mometasone at visit 5 (sequence 2). Randomisation was accomplished using a validated system (SAS 8.1) that automates random assignment of treatment sequence to randomisation number.

At visits 3 and 5, subjects were exposed to grass pollen not currently in season at the investigative site (mixture of equal amounts of dactylis glomerata, lolium perenne, phleum pratense) in the VCC under standardised conditions (2000 grains/m\(^3\), 33% humidity, 24°C temperature) over an 8-hour period. After 2 hours of pollen exposure, appropriate site personnel not involved in the study assessments...
instilled one drop of ketotifen or vehicle placebo in each eye and administered two puffs per nostril of mometasone. To maintain masking, ketotifen and placebo were individually packaged, and bottles were identical in appearance and construction. No randomisation codes were broken during the trial.

Every 15 minutes throughout the postdosing period of allergen challenge in the VCC (hours 2–8), subjects rated the severity of the following signs and symptoms: ocular itching, tearing, foreign body sensation, redness, stiffness, sneezing, nasal itching, and running nose. Each sign and symptom was rated using a standardised 4-point ordinal scale ranging from 0 to 3, with higher scores indicative of greater severity. From these parameters, composite scores for ocular and nasal signs and symptoms were calculated.

Study Population

Subjects (male or female, any ethnicity) had to meet the following main criteria to participate in the study: (i) provide written informed consent; (ii) be ≥18 years of age; (iii) have at least a 2-year history of SARC, but essentially asymptomatic at screening; (iv) have a positive skin prick test or radioallergosorbent test obtained within the last 2 years; and (v) have a composite ocular symptom score ≥4 at baseline (with an itching score ≥2 within the 2-hour challenge period in the VCC before instillation of study medication). The main exclusion criteria were: (i) ocular surgical intervention within 3 months before or during the trial; (ii) glaucoma, retinal disease or diagnosis of dry eye; (iii) an active bacterial or viral ocular infection; and (iv) use of contact lenses during the treatment period and within 2 days of enrolment. The majority of study participants were previously involved in other studies, where they had demonstrated good reactivity to the grass pollen used in this study.

Efficacy and Safety Criteria

Individual and composite symptom-relief scores were calculated as differences between baseline scores (severity of a sign or symptom just prior to instillation of masked medication at visits 3 and 5) and each of the postdose scores. The area under the curve (AUC) of the symptom-relief scores over time allowed a baseline-corrected comparison of efficacy, in which a larger AUC value indicated better symptom relief.

The primary efficacy variable was the mean AUC of symptom relief 4–6 hours postdose (AUC4–6) for ocular itching. The 4- to 6-hour postdose period was selected to reduce a potential washing effect by vehicle placebo following instillation. AUC values were also calculated and analysed for the entire 6-hour postdosing period (AUC0–6) and for the remaining 2-hour increments (AUC0–2 and AUC2–4). Secondary efficacy variables included AUC values of the individual (except itching) and composite ocular and nasal symptom relief scores for the 0- to 2-, 2- to 4-, 4- to 6- and 0- to 6-hour postdosing periods.

Safety was based on slit-lamp biomicroscopy conducted before and after allergen challenge at visits 3 and 5; vital signs (brachial artery blood pressure and radial pulse) taken at visits 3 and 5 before and after allergen challenge; and adverse event monitoring at visits 2 through 5.

Statistical Analysis

A sufficient number of subjects were to be randomised to achieve the goal of at least 40 subjects (20 subjects per treatment sequence) completing the study. No interim or subgroup analyses were planned or performed. All analyses were conducted on an intent-to-treat basis using data from all randomised subjects who received at least one dose of study medication. No data were imputed for missing values. All statistical tests were two-sided, and tests with a corresponding probability (p) value ≤0.05 were considered statistically significant.

For demographic and baseline characteristics, between-treatment sequence comparisons were analysed using Fisher’s Exact Test for binary and unordered categorical variables and a Wilcoxon rank sum test for continuous variables.

All AUC values were calculated using the trapezoidal rule. An analysis of variance (ANOVA) model was used to test differences between treat-
ments for the efficacy analyses, with treatment, period and subject as factors. The null hypothesis was that there was no difference between the two treatments (ketotifen and placebo) in mean AUC values. The alternative hypothesis was that there was a difference (two-sided alternative) between treatments.

Summary statistics were used to present changes from baseline in vital signs by treatment. Notable abnormalities in slit-lamp results were flagged and described. Treatment-emergent adverse events were described.

Results

Disposition, Demographics and Baseline Characteristics

A total of 47 subjects were enrolled and randomised to treatment. Of these, 24 subjects were randomised to sequence 1 and 23 were randomised to sequence 2. Forty-four subjects (94%) completed the study as planned. Three (6%) subjects discontinued prematurely due to either an adverse event (one subject) or protocol violation (two subjects). Each protocol violation consisted of an ocular symptom score at the baseline of visit 5 that fell below the minimum set by the protocol.

Demographics and baseline characteristics were comparable between the two treatment sequences; no statistically significant differences were observed. Overall, approximately half of the subjects were female (51%), and all were Caucasian. Mean age was 26.5 years (range 20–45 years). Most subjects had no past medical history (89%), and the majority had no current medical condition at entry (62%).

All subjects received masked study medication as allocated. The efficacy analyses included data from 47 subjects at visit 3 and 44 subjects at visit 5. All randomised and treated subjects were evaluated for safety (n = 47).

Efficacy Findings

After 2 hours of exposure in the VCC (i.e. at baseline), mean ocular and nasal sign and symptom scores were comparable between subjects assigned to the two adjunctive treatments (table I).

Use of ketotifen adjunctive to mometasone resulted in significant improvement in ocular itching from baseline within 15 minutes of dosing, which was maintained throughout VCC exposure. A less marked improvement from baseline was also observed with adjunctive use of placebo. Improvement in ocular itching was significantly better with ketotifen than with placebo adjunctive to mometasone (figure 2). Mean AUC4-6 values for relief of ocular

Table I. Mean baseline scores for the signs and symptoms of rhinoconjunctivitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mometasone + placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 46)</td>
</tr>
<tr>
<td>Ocular itching</td>
<td>2.11 ± 0.67</td>
</tr>
<tr>
<td>Other ocular signs and symptoms</td>
<td></td>
</tr>
<tr>
<td>Tearing</td>
<td>1.30 ± 0.87</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>1.85 ± 1.01</td>
</tr>
<tr>
<td>Conjunctival redness</td>
<td>1.79 ± 0.79</td>
</tr>
<tr>
<td>Ocular composite score</td>
<td>7.04 ± 2.67</td>
</tr>
<tr>
<td>Nasal signs and symptoms</td>
<td></td>
</tr>
<tr>
<td>Stiffness</td>
<td>1.99 ± 0.68</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.80 ± 0.75</td>
</tr>
<tr>
<td>Itching nose</td>
<td>1.98 ± 0.58</td>
</tr>
<tr>
<td>Running nose</td>
<td>1.89 ± 0.67</td>
</tr>
<tr>
<td>Nasal composite score</td>
<td>7.65 ± 1.74</td>
</tr>
</tbody>
</table>

a Severity of each sign and symptom was evaluated by the subject using a 4-point ordinal scale ranging from 0 (none) to 3 (severe).
b Mean scores were calculated over visits 3 and 5 for each adjunctive therapy.
Itching were 144.27 and 103.47 with ketotifen and placebo, respectively (p = 0.014). Significant between-treatment differences in favour of mometasone + ketotifen were also observed for improvement in ocular itching from 0–2 hours postdose (p = 0.006) and 0–6 hours postdose (p = 0.009). The difference between adjunctive treatments for the 2- to 4-hour postdose period nearly achieved statistical significance in favour of mometasone + ketotifen (p = 0.058).

With regard to other ocular signs and symptoms, mean AUC4–6 values for reduction of tearing (p = 0.029), conjunctival redness (p = 0.005), and the ocular composite score (p = 0.005) were all significantly in favour of mometasone + ketotifen (figure 3). Significant superiority of ketotifen to placebo adjunctive to mometasone (p ≤ 0.050) for improvement in conjunctival redness and for the reduction of the ocular composite score was also observed at other postdose time intervals. The effect of adjunctive therapy on reducing foreign body sensation was not significantly different between treatments (figure 3).

In addition to its ocular effects, ketotifen was also superior to placebo adjunctive to mometasone in alleviating the nasal signs and symptoms of rhinoconjunctivitis. Mean AUC4–6 values for improvement in sneezing (p = 0.008), running nose (p = 0.018), and the nasal composite score (p = 0.006) were significantly in favour of mometasone + ketotifen (figure 4). Similar results were also observed at other postdose time intervals. Between-treatment differences for stuffiness and nasal itching did not reach statistical significance (figure 4).

Safety Findings

Only one subject experienced a treatment-emergent adverse event during the study. This event (pharyngitis) was mild in intensity and not attributed to study drug by the investigator. The subject was withdrawn from the trial at visit 5 prior to entering the VCC. None of the slit-lamp and vital sign evaluations were indicative of a safety concern for the combined use of mometasone nasal spray and ketotifen eye drops.

Discussion

Since allergic rhinoconjunctivitis is a multifactorial disease, combination therapies are often re-
Fig. 4. Improvements in nasal signs and symptoms during allergen exposure. Based on analysis of variance, statistical significance (*) was observed between adjunctive therapies in favour of ketotifen for AUCCₐ evaluations of sneezing (p = 0.006), running nose (p = 0.018), and the nasal composite score (p = 0.006). A larger number indicates better symptom relief. AUCCₐ = mean area under the curve of symptom relief 4-6 hours postdose.

required to alleviate all signs and symptoms associated with the condition. Treatment strategies should be designed to manage all aspects of the disorder and address one or more of the molecular mechanisms involved in the pathogenesis of the disease. Moreover, topical formulations that directly target involved sites, namely the eyes and nose, are recommended to limit unwanted systemic effects that may occur with oral therapy.\textsuperscript{[6]} Ketotifen combines the pharmacological actions of both antihistamines and mast cell stabilisers and, in addition, inhibits eosinophil chemotaxis, activation and degranulation.\textsuperscript{[13-15,23,24]} Together with an excellent safety and tolerability profile,\textsuperscript{[25]} ketotifen eye drops are an ideal candidate for use as ocular treatment adjunctive to nasal therapy in subjects with allergic rhinoconjunctivitis. The VCC allows evaluation of therapy in allergic subjects provoked with environmental concentrations of the offending pollen allergen under controlled conditions. However, to prove the efficacy of a drug therapy in this model, it is essential that subjects develop moderate to severe symptoms upon pollen challenge in order to observe significant treatment effects with a reasonable sample size.

Results of this study demonstrated that ketotifen 0.025% eye drops are an effective adjunctive therapy to mometasone 50µg nasal spray in individuals with seasonal allergic rhinoconjunctivitis. Combined use of mometasone + ketotifen reduced the severity of ocular itching (the primary efficacy variable) significantly better than mometasone + placebo. Similarly, ketotifen adjunctive to mometasone was significantly superior to mometasone monotherapy in reducing the severity of tearing and conjunctival redness during allergen challenge.

In addition to the ocular effects, ketotifen also improved the nasal symptoms commonly associated with the allergic response (i.e. sneezing and rhinorrhoea). In fact, ketotifen 0.025% eye drops in combination with mometasone showed a statistically significant improvement in most nasal symptom scores (sneezing, running nose and nasal composite) compared with mometasone alone. Relief occurred within 1 hour of dosing. Significant improvements in both ocular and nasal composite scores further illustrate that adjunctive therapy with ketotifen eye drops provides better control of all signs and symptoms of allergic rhinoconjunctivitis than monotherapy with mometasone nasal spray. The additional effect of ketotifen eye drops on nasal symptoms may be due to the drug’s activity on the mucous membrane of the nose by draining down the nasolacrimal duct. Furthermore, the reduction of tearing by the active treatment leads to a reduction of nasal blockage induced by tears. As a result, patients complain less about their ocular symptoms and tend to score their nasal symptoms lower.\textsuperscript{[19]}

Safety results from this study suggest that the combined use of mometasone nasal spray and ketotifen eye drops is safe.

**Conclusion**

In conclusion, ketotifen eye drops adjunctive to mometasone nasal spray provided greater relief of both ocular and nasal allergy signs and symptoms than mometasone alone. Together with an excellent safety and tolerability profile, ketotifen eye drops
are an ideal adjunctive therapy to mometasone nasal spray in individuals with seasonal allergic rhinoconjunctivitis.

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References


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