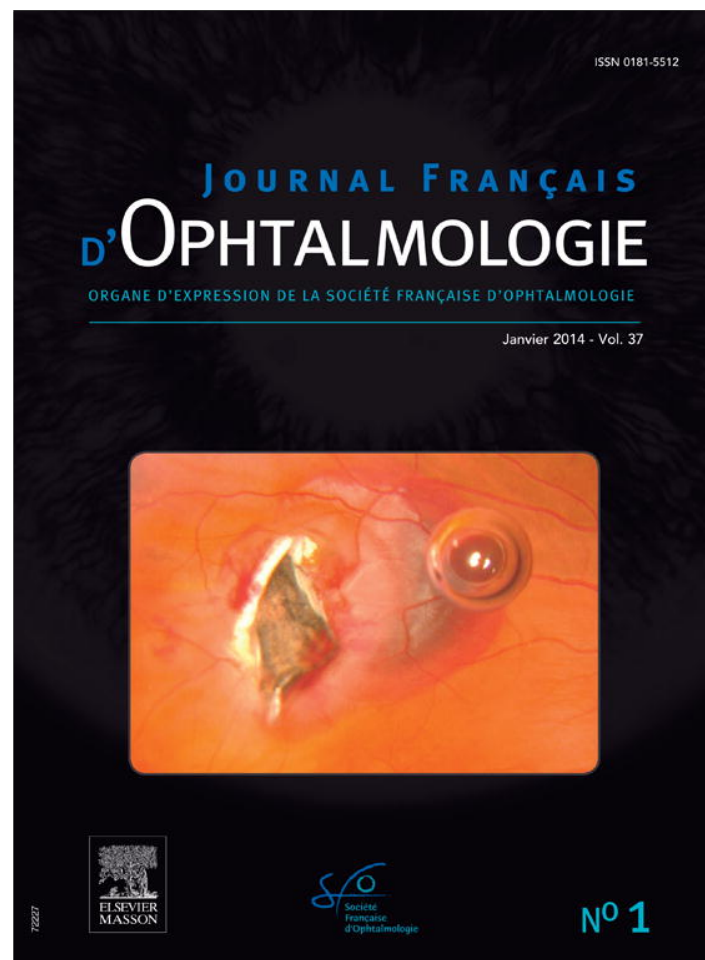




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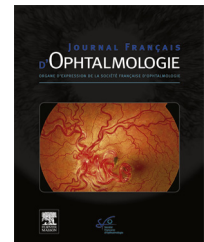
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ORIGINAL ARTICLE

Comparison of preservative-free ketotifen fumarate and preserved olopatadine hydrochloride eye drops in the treatment of moderate to severe seasonal allergic conjunctivitis



Comparaison du collyre de kétotifène fumarate sans conservateur et du collyre d'olopatadine hydrochloride conservé dans le traitement de la conjonctivite allergique saisonnière modérée à sévère

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KEYWORDS

ICAM-1;
Ketotifen;
Olopatadine;
Seasonal allergic
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MOTS CLÉS

ICAM-1 ;
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Olopatadine ;
Conjonctivite
allergique
saisonnière ;
Conservateur

Summary

Purpose. — To compare preservative-free ketotifen 0.025% ophthalmic solution to olopatadine 0.1% ophthalmic solution in with the treatment of seasonal allergic conjunctivitis (SAC) in clinical practice.

Methods. — This was a comparative, randomised, investigator-masked, pilot clinical study in adult patients with documented history of SAC and presenting with moderate to severe itching and conjunctival hyperemia. Eligible patients initiated either ketotifen or olopatadine treatment at a dose of one drop twice daily for 28 days. The resolution of ocular signs and symptoms was assessed on day 7 and day 28. Itching was also assessed within 15 minutes following the first instillation (day 0). Conjunctival impression cytology was performed at each visit to assess the evolution of ICAM-1 expression (day 0, 7 and 28).

Results. — Seventy-five patients were randomised (ketotifen: 38 patients; olopatadine: 37 patients). At day 28, the composite score for primary criteria (itching, tearing, and conjunctival hyperemia) improved from 6.8 ± 1.2 to 0.9 ± 1.0 in the Ketotifen group, without statistically significant difference between treatment groups ($P=0.67$). There was no relevant difference between treatment groups in other efficacy parameters, except a trend for a more rapid resolution of conjunctival hyperemia in the Ketotifen group. Both drugs were well tolerated, with a trend for a better tolerability reported by patients on ketotifen compared to those on olopatadine at day 7 ($P=0.054$).

Conclusions. — A rapid and comparable improvement in SAC was achieved after 28 days of treatment with both preservative-free ketotifen and preserved olopatadine ophthalmic solutions, with a slightly better ocular tolerance with unpreserved ketotifen 0.025% eye drops.

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Résumé

Objectif. — Comparer les collyres de kétotifène 0,025 % sans conservateur et d'olopatadine 0,1 % dans le traitement de la conjonctivite allergique saisonnière (CAS) en pratique clinique.

Méthodes. — Cette étude pilote, comparative, randomisée, en simple insu, a été réalisée chez des patients adultes avec antécédents de CAS et présentant un prurit oculaire et une hyperémie conjonctivale modérés à sévères. Les patients inclus s'instillaient une goutte de kétotifène ou d'olopatadine deux fois par jour durant 28 jours. L'amélioration des symptômes et signes oculaires a été évaluée à j7 et j28. L'évolution du prurit oculaire a été évaluée durant les 15 minutes après la première instillation. Le taux du marqueur biologique ICAM-1 a été mesuré sur des prélèvements d'empreintes conjonctivales effectuées à chaque visite (j0, j7 et j28).

Résultats. — Soixante-quinze patients ont été randomisés (kétotifène : 38 patients ; olopatadine : 37 patients). À j28, le score composite du critère primaire (associant prurit, larmolement, et hyperémie conjonctivale) a été réduit de $6,8 \pm 1,2$ à $0,9 \pm 1,0$ dans le groupe Kétotifène, sans différence significative entre les groupes de traitement ($p=0,67$). Concernant les autres paramètres d'efficacité, seule une tendance à l'amélioration plus rapide de l'hyperémie conjonctivale a été observée dans le groupe Kétotifène. Les deux traitements ont été bien tolérés, avec une tendance à une meilleure tolérabilité du collyre de kétotifène comparativement au collyre d'olopatadine à j7 ($p=0,054$).

Conclusion. — Une amélioration rapide et comparable des symptômes/signes de la CAS a été obtenue après 28 jours de traitement avec un collyre de kétotifène non conservé et un collyre d'olopatadine ; avec une tolérance oculaire légèrement meilleure rapportée pour le collyre de kétotifène non conservé.

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Introduction

Seasonal allergic conjunctivitis (SAC) is an inflammatory response of the conjunctiva triggered by exposure to seasonal allergens. With an estimated prevalence of approximately 15 to 20%, SAC is the most common form of ocular allergy [1]. The distressing signs and symptoms of SAC may cause extreme discomfort, with a burden due to the frequency and duration of the disease more than to seriousness.

Upon exposure to a specific allergen, allergic patients elicit a hypersensitivity response, which may take minutes or even days to manifest. SAC is a type 1 mast cell dependent IgE mediated immune hypersensitivity reaction. Exposure to environmental antigens stimulates the immune system resulting in mast cells sensitisation. Sensitised mast cells initiate degranulation releasing a cascade of allergic and inflammatory mediators responsible for the inflammatory response [2,3]. Histamine is the cardinal mediator responsible for the early signs and symptoms of SAC, as its H1

and H2 receptor binding activates nerve cells and endothelial cells [3,4]. Other mediators released by mast cells are responsible for sustaining the late phase of the ocular allergic reaction [5]. The late phase (2 to 24 hours after allergen exposure) results from the infiltration and activation of inflammatory eosinophils and macrophages. The pathognomonic symptom of ocular allergy is itching; other main symptoms are ocular redness, tearing, chemosis, and swelling [6]. Besides, the proinflammatory involvement of ocular surface cells has been reported, as well as the role of the expression of intercellular adhesion molecule-1 (ICAM-1) in this recruitment [7,8]. Blocking of the histamine receptor was shown to down-regulate ICAM-1 expression, resulting in anti-inflammatory effects [9,10].

The main anti-allergy topical agents for SAC are antihistamines and mast-cell stabilizers [6,11]. Topical anti-allergic medications such as ketotifen and olopatadine eye drops possess at least dual mechanism of action combining antihistamine and mast cell stabilization effects, and are today ideal topical agents for treatment of SAC [6,12]. They provide both a rapid symptomatic relief resulting from the immediate histamine receptor antagonism, and a long-term disease-modifying benefit of mast cell stabilization. In addition, ketotifen fumarate was shown to present anti-inflammatory effects in preventing eosinophil accumulation and activation [13,14].

Comparative studies based on conjunctival allergen challenge (CAC) or conducted in an environmental setting have shown that both ketotifen and olopatadine eye drops are safe and effective [8,11,15–18]. However, the relief of ocular signs and symptoms, overall judgement of treatment efficacy (by the patient or investigator), and ocular comfort upon instillation may differ between the two agents [7,19–22]. This study aimed at assessing the efficacy and safety of preservative-free ketotifen fumarate in the treatment of SAC in comparison with olopatadine hydrochloride eye drops after 1-month treatment and the conjunctival surface inflammation using the conjunctival ICAM-1 expression level.

Patients and methods

This pilot, comparative, multicentre, randomised, investigator-masked, two-parallel groups, clinical study was conducted between May and November 2011 in France (six ophthalmologic centres) and Tunisia (four centres). Male or female patients superior or equal to 18 years old with documented history of SAC were included when they showed moderate to severe ocular itching and hyperaemia. Patients with other associated ocular pathologies or history of ocular diseases potentially interfering with SAC assessments (i.e., superficial punctate keratitis, cornea ulcer, vernal keratoconjunctivitis, severe progressive rosacea, ocular herpes, infectious keratitis, uveitis, eyelid dysfunction), as well as ocular anomalies interfering with ocular surface, were not included in the study.

The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and local regulations. Ethics committee approvals were obtained in each country prior to enrolling any patient and written informed consent was obtained from each patient.

Eligible patients were randomly assigned to one of the study medications according to a computer-generated randomisation code list (1:1 ratio). Patients were randomised on day 0 either in the Ketotifen group (ketotifen fumarate 0.025% eyedrops, packaged in multi-dose Abak® container, without preservative) or the Olopatadine group (olopatadine hydrochloride 0.1% eyedrops, packaged in multi-dose container, with preservative). Patients were treated for 28 days with one drop of the study medication twice a day in each eye (with an 8-hour interval between two instillations). Other medications during the study including corticosteroids, non-steroidal anti-inflammatory drugs, other oral or topical antihistamines, and any treatment which could affect the lachrymal function, were not allowed.

For masking purpose, two investigators were involved: a first investigator was in charge of patient selection and ophthalmic assessments and remained masked of study treatments, and the second investigator was responsible for dispensing medication and retrieving the product from the patient. Patients were assessed during a baseline (day 0), follow-up (day 7), and final (day 28) visit. At each visit, itching was scored using a 5-point scale (from 0 = absent to 4 = incapacitating), while other clinical signs/symptoms (tearing, burning/stinging, conjunctival hyperaemia, chemosis, eyelids swelling, superficial punctate epithelial keratitis, and other ocular abnormality at slit lamp examination) were assessed using a 4-point scale (from 0 = none to 3 = severe; see grading scales used in the legend of Table 1).

Itching and ocular discomfort, scored by the patient using a visual analogic scale (VAS), were assessed at 3, 7 and 15 minutes following the first instillation (day 0). The global efficacy was assessed on day 7 and day 28, by the patient as excellent (complete or almost complete relief of ocular allergy symptoms), good (distinct relief of ocular allergy symptoms), fair (some relief from ocular allergy symptoms), poor (no relief from ocular allergy symptoms), or deterioration (worsening of ocular allergy symptoms), and by the investigator as very satisfactory, satisfactory, not very satisfactory, or unsatisfactory. The response rate was defined as a global efficacy score rated as excellent or good by the patients.

Safety evaluations included ocular and systemic adverse event reporting, visual acuity, and overall local tolerance assessed by the first investigator using a 4-point scale (from very satisfactory to unsatisfactory), and the patient.

At each visit, the first investigator collected conjunctival impression specimens under topical anaesthesia (0.4% oxybuprocaine), using two strips of 0.2 µm Supor® PES (polyethersulfone) membranes applied onto the upper conjunctival surface. Detection of the ICAM-1 was performed using indirect immunofluorescence and flow cytometric analysis, as described previously [23].

Statistical analysis

Statistical analyses were carried out on the SAS Software, release 9.1.3 (SAS Institute NC, Cary, USA). For the data recorded in both eyes the analyses were performed on the most pathological eye at baseline (worst eye). Analyses were performed on the intent-to-treat (ITT; all treated patients

with at least one post-baseline efficacy assessment) and per protocole (PP; all ITT patients without major protocol deviation) populations. The primary efficacy criteria was the ocular primary composite endpoint day 28 calculated by adding itching, tearing, and conjunctival hyperaemia scores. If day 28 value was missing, a "last observation carried forward" (LOCF) method was used for the primary criterion. The changes from baseline were estimated with their 95% confidence interval (95% CI) and compared between groups using an analysis of covariance (ANCOVA) with baseline as a covariate. The conjunctival impression cytology was described at each time in log10 transformation of arbitrary units of fluorescence in patients with detectable and interpretable levels of ICAM-1. Difference between groups was assessed using an ANCOVA. Other variables were compared between groups using the Cochran-Mantel-Haenszel (CMH) test for ordinal variables or using Chi-square test or

Table 1 Ocular signs and symptoms in the worst eye at baseline.

	Ketotifen <i>n</i> = 38	Olopatadine <i>n</i> = 37
<i>Itching</i>		
0	—	—
1	—	—
2	—	—
3	31 (81.6%)	30 (81.1%)
4	7 (18.4%)	7 (18.9%)
<i>Conjunctival hyperaemia</i>		
0	—	—
1	—	—
2	28 (73.7%)	27 (73.0%)
3	10 (26.3%)	10 (27.0%)
<i>Tearing</i>		
0	2 (5.3%)	2 (5.4%)
1	23 (60.5%)	16 (43.2%)
2	10 (26.3%)	15 (40.5%)
3	3 (7.9%)	4 (10.8%)
<i>Irritation/burning</i>		
0	—	—
1	14 (36.8%)	13 (35.1%)
2	19 (50.0%)	17 (45%)
3	5 (13.2%)	7 (18.9%)
<i>Stinging</i>		
0	—	—
1	16 (42.1%)	10 (27.0%)
2	20 (52.6%)	23 (62.2%)
3	2 (5.3%)	4 (10.8%)
<i>Chemosis</i>		
0	26 (68.4%)	22 (59.5%)
1	10 (26.3%)	13 (35.1%)
2	2 (5.3%)	2 (5.4%)
3	—	—
<i>Eyelid swelling</i>		
0	25 (65.8%)	24 (64.9%)
1	9 (23.7%)	10 (27.0%)
2	3 (7.9%)	2 (5.4%)

Table 1 (Continued)

	Ketotifen <i>n</i> = 38	Olopatadine <i>n</i> = 37
3	1 (2.6%)	1 (2.7%)
Ocular symptoms and signs were scored using the following grading scales: Itching: 0 = none, 1 = mild (intermittent tickling sensation), 2 = moderate (continual awareness without the desire to rub), 3 = severe (continual awareness with the desire to rub), 4 = incapacitating (insisting on rubbing eyes); conjunctival hyperaemia: 0 = absent, 1 = mild (some vessels injected above normal), 2 = moderate (diffusely red eye with individual vessels dilated but not discernible), 3 = severe (intensely red eye with intensive dilation of conjunctival vessels); tearing: 0 = absent, 1 = mild (eye slightly watery), 2 = moderate (blowing nose occasionally), 3 = severe (tears rolling down the cheeks); irritation/burning/stinging: 0 = absent, 1 = mild (present but not disturbing), 2 = moderate (disturbing, but not interfering with daily activities), 3 = severe (very distressing and interfering with daily activities); chemosis: 0 = none, 1 = mild (visually evident, raised conjunctiva, especially in limbal area), 2 = moderate (ballooning of the conjunctiva), 3 = severe (severe ballooning of the conjunctiva); eye swelling: 0 = absent, 1 = mild (lids are a little puffy), 2 = moderate (distinct swelling of upper and lower eyelids), 3 = severe (eyelids are swollen).		

Fisher exact test for binary variables. All statistical tests were performed two-sided, at the 5% level of significance.

Results

Seventy-five patients (mean age: 47 years) were enrolled and randomised in the study: 38 patients in the Ketotifen group and 37 patients in the Olopatadine group (Table 2). All but two (one in each treatment group) patients completed the study. Major protocol deviations which could interfere with the study results were reported for nine patients (five patients in the Ketotifen group, and four in the Olopatadine group). Major protocol deviations mainly related to the non-respect of treatment compliance/duration (*n* = 4) and occurrence of concomitant pathologies (*n* = 3) no related to the study medications.

At baseline (day 0), there was no relevant difference in patients' characteristics between treatment groups

Table 2 Patients' baseline characteristics.

	Ketotifen <i>n</i> = 38	Olopatadine <i>n</i> = 37
<i>Age (years)</i>		
Mean ± SD	47.2 ± 18.6	46.6 ± 18.5
(Min–Max)	(19–76)	(19–75)
<i>Gender</i>		
Male, <i>n</i> (%)	11 (28.9%)	13 (35.1%)
Female, <i>n</i> (%)	27 (71.1%)	24 (64.9%)
<i>Time since diagnosis of SAC (years)</i>		
Mean ± SD	4.7 ± 4.9	5.6 ± 8.2
Median	2.8	2.6
(Min–Max)	(0.0–21.7)	(0.0–41.8)

(Table 2). The median duration of SAC history was 2.7 years, ranging from 0 to 42 years. Regardless of treatment group, itching was severe in 81% of patients and incapacitating in 19% (Table 1); conjunctival hyperaemia was moderate in 73% of patients and severe in 27%. Tearing was slightly more frequently rated as moderate/severe in the Olopatadine group (51.3% of patients) than in the Ketotifen group (34.2%). Other ocular signs or symptoms in the worst eye were reported similarly in both groups except stinging rated more frequently as moderate/severe in the Olopatadine group compared to the Ketotifen group. SPK was moderate or severe in two patients (5.4%) in the Olopatadine group. Other ocular abnormality was reported in one patient in the Ketotifen group (moderate conjunctival papillae in both eyes).

On day 28, there was a marked decrease in the ocular composite score without statistically significant difference between groups ($P=0.67$; Table 3). The estimated changes [95% CI] from baseline was -6.04 [-6.40 ; -5.68] in the Ketotifen group and -5.93 [-6.29 ; -5.57] in the Olopatadine group. Similar results were shown in the contralateral affected eye and PP analysis (data not shown).

The evolution from baseline in each component of the ocular composite score in the worst eye is illustrated in Fig. 1. Changes in itching were similar in both treatment groups at day 7 and day 28. In the Ketotifen group, itching was mild or absent in 79% of patients on day 7 (versus 81% in the Olopatadine group) and in 97% of patients on day 28 (vs. 92% in the Olopatadine group). Although the difference between treatment groups was not statistically significant, there was a trend for a better resolution of conjunctival hyperaemia in the Ketotifen group on day 28, as a complete resolution of conjunctival hyperaemia concerned more patients in the Ketotifen (70%) than in the Olopatadine (59%) group. No difference in the resolution of tearing was noted between groups: tearing was mild or absent in 94% of patients on day 7 in the Ketotifen group (vs. 97% in the Olopatadine group) and in 97% of patients on day 28 (vs. 97% in the Olopatadine group). No difference between treatment groups was also observed for the resolution of other signs and symptoms (data not shown).

Assessment of itching following the first instillation is illustrated in Fig. 2. Overall, there was a rapid post-instillation improvement in itching, without statistically significant difference between treatment groups after 3, 7 and 15 minutes. The itching severity was significantly improved as soon as 3 minutes post-instillation in both treatment groups, with only about one third of the patients still experiencing severe or incapacitating itching (39% vs. 33% in the Ketotifen and Olopatadine group, respectively). A rapid decrease in global ocular discomfort evaluated on VAS was also reported, with no difference between groups (from -16.7 vs. -19.1 mm at 3 minutes to -23.4 vs. -23.6 mm at 15 minutes post-instillation in the Ketotifen and Olopatadine group, respectively).

There were no significant differences between groups in the response rate assessed by the patient, as well as in the global efficacy assessed by the investigator: the responder rate was 76.3% vs. 73.0% on day 7, and 89.2% vs. 86.5% on day 28, respectively, in the Ketotifen and Olopatadine group; the investigator considered the ketotifen and olopatadine treatment as very satisfactory/satisfactory, respectively, in

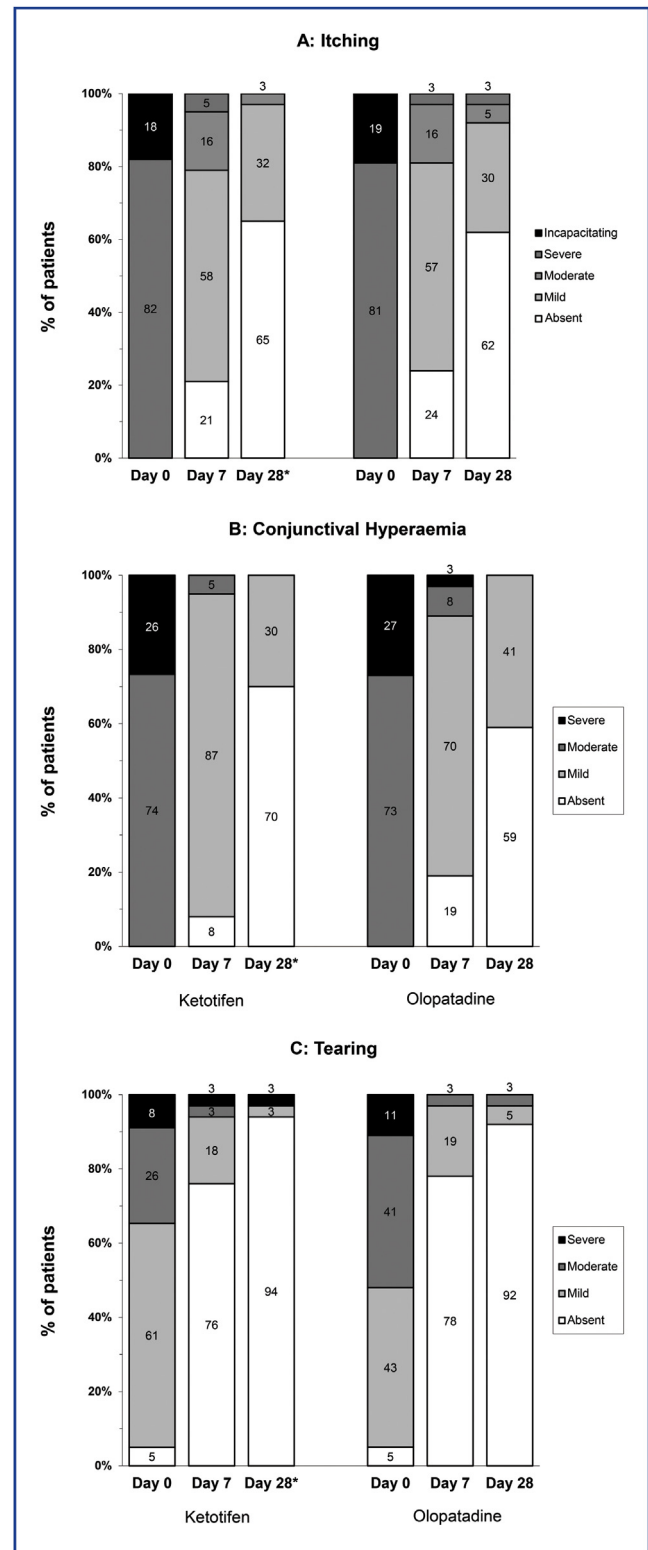


Figure 1. Evolution of each component of the ocular composite score in the worst eye (intent-to-treat population, ITT). Each sign or symptom were rated by the investigator or the patients at each visit using a 5-point (itching) or 4-point (conjunctival hyperaemia, tearing) scoring scale (see description of scoring scales in the legend of Table 1). *: one patient in the Ketotifen group was not assessed on day 28.

Table 3 Evolution of the ocular composite score in the worst eye between day 0 and day 28.

	Ketotifen <i>n</i> = 38	Olopatadine <i>n</i> = 37
Day 0 (mean ± SD)	6.8 ± 1.2	7.0 ± 1.4
Day 28 (mean ± SD)	0.9 ± 1.0	1.0 ± 1.2
Change from baseline (D28-D0)	−5.9 ± 1.6	−6.0 ± 1.6
Statistical analysis (ANCOVA)		
Estimated difference within group [95% CI]	−6.04 [−6.40; −5.68]	−5.93 [−6.29; −5.57]
Estimated difference ^a between groups [95% CI]	−0.11 [−0.62; 0.40]	
<i>P</i> value	<i>P</i> = 0.67	

^a Ketotifen - olopatadine.

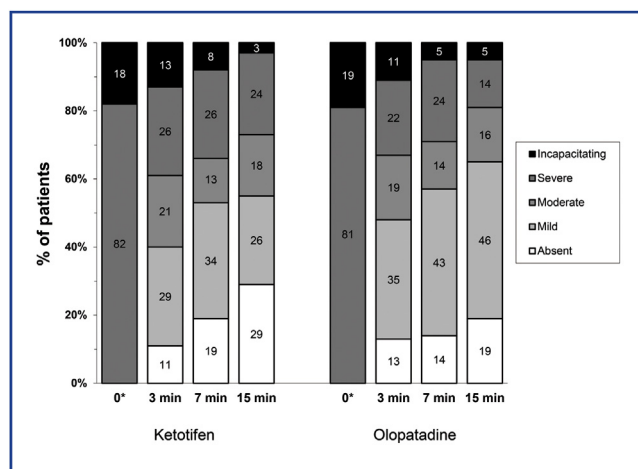


Figure 2. Evolution of itching following the first instillation (ITT Population). Itching was rated by the patients using the 5-point scale (see legend of Table 1) prior to instillation (*), and then 3, 7, and 15 minutes post-instillation.

89% vs. 92% of patients on day 7, and 95% vs. 97% of patients on day 28.

The ICAM-1 expression was analyzed in 14 ketotifen-treated and 19 olopatadine-treated patients with detectable and interpretable protein expression level. On day 28, the expression level of ICAM-1 was similarly decreased in both treatment groups (Table 4). The difference between group was not statistically significant ($P=0.44$). The relative decrease from baseline was 16.1% (95% CI = [4.1; 29.4]) in the Ketotifen group and 8.8% (95% CI = [2.13; 19.6]) in the Olopatadine group.

Both products were well tolerated. Two patients in the Ketotifen group and one patient in the Olopatadine group experienced a non-ocular adverse event during treatment (tonsillitis or bronchitis). Ocular adverse events were reported in one patient in the Ketotifen group (conjunctival inflammation) and two patients in the Olopatadine group (viral conjunctivitis and new confirmed allergic conjunctivitis). There was no change in visual acuity in both treatment groups. The overall tolerance assessed by the investigators on day 28 was very satisfactory/satisfactory

in 100% of patients treated with ketotifen vs. 95% of patients treated with olopatadine. Slightly more patients in the Ketotifen group found the treatment tolerable on day 7 (100.0% vs. 89.2% in the Olopatadine group; $P=0.054$) and day 28 (97.3% vs. 86.5% in the Olopatadine group; $P=0.199$). One patient in the Ketotifen group (2.6%) complained of mild burning/stinging upon instillation, while five patients in the Olopatadine group (13.5%) experienced symptom(s) upon instillation: four patients (10.8%) complained of mild/moderate irritation/burning/stinging, one patient (2.7%) of eye dryness sensation, and one patient (2.7%) of foreign body sensation.

Discussion

This 1-month environmental study was intended to compare in clinical settings two dual-mechanism (antihistamine and mast cell stabilizer combination) anti-allergy topical agents, i.e., ketotifen fumarate 0.025% and olopatadine hydrochloride 0.1%, in the treatment of SAC.

Efficacy assessments of SAC therapy are based on a number of symptoms (itching, tearing, irritation/burning, and stinging) and signs (conjunctival hyperaemia, chemosis and eyelid swelling). Among the main signs and symptoms of ocular allergy, conjunctival hyperaemia, itching and tearing have been shown to be the most severe and frequent in several environmental studies [7,19,21]. For the present pilot phase II study, these three targets of SAC treatment have been combined in a composite efficacy outcome. Primary composite outcomes are frequently used in trials assessing anti-allergy drugs, the main argument supporting this approach being to increase statistical precision due to higher event rates, without requiring huge sample sizes [24].

Numerous clinical studies published on the efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution were based on the CAC model. As single-dose model, the CAC model offers a standardisation of the allergic reaction, but there is a detachment from “real world” which may be prejudicial to patient assessment of efficacy and tolerance. Furthermore, environmental studies, now preferred by health authorities, allow longer-term assessment of anti-allergic treatments [13]. In a previous 3-week comparative study of ketotifen fumarate 0.025% and olopatadine

Table 4 Evolution of ICAM-1 conjunctival expression (log10) between day 0 and day 28.

	Ketotifen <i>n</i> = 14	Olopatadine <i>n</i> = 19
Day 0 (mean ± SD)	3.49 ± 0.50	3.53 ± 0.39
Day 28 (mean ± SD)	2.90 ± 0.90	3.12 ± 0.73
Change from baseline (D28-D0)	−0.59 ± 0.95	−0.40 ± 0.99
Statistical analysis (ANCOVA)		
Estimated difference within groups [95% CI]	−0.61 [−1.06; −0.17]	−0.38 [−0.77; −0.00]
Estimated difference ^a between groups [95% CI]	−0.23 [−0.82; 0.36]	
<i>P</i> value	<i>P</i> = 0.43	
Relative change from baseline (D28-D0) (%)	−16.1 ± 25.0	−9.2 ± 27.7
Statistical analysis (ANCOVA)		
Estimated difference within groups [95% CI]	−16.7 [−29.4; −4.1]	−8.8 [−19.6; 2.1]
Estimated difference ^a between groups [95% CI]	−8.0 [−24.7; 8.7]	
<i>P</i> value	<i>P</i> = 0.34	

^a Ketotifen - olopatadine.

hydrochloride 0.1%, Ganz et al. showed a significantly stronger improvement of SAC with ketotifen using a wider but comparable composite outcome, as only three signs and symptoms were really active, namely conjunctival hyperaemia, itching and tearing [21]. Compared to our study, the main difference was the severity of the composite score at baseline, which was about twice lower in this study (6.9 versus 3.3). Regarding individual components of the composite efficacy outcome at inclusion, itching was the most severe symptom in both studies, but the severity of all three symptoms/sign, particularly conjunctival hyperaemia, was definitely higher in our study. Unlike the present trial, moderate to severe conjunctival hyperaemia (score ≥ 2) was not defined as an inclusion criterion in the study by Ganz et al. [21], in which patients barely experienced this sign at baseline. Moreover, context of the two studies was different, as patient inclusion started in May 2011 during the pollen season in our study, while it took place during the fall pollen season (August–October) in a distinct area (Midwestern United States) in the other study [21]. Interestingly, in two other previous comparative environmental studies performed during the peak pollen season (April–May) in Turkey, no significant differences in sign and symptom improvements were found between ketotifen and olopatadine [7,19]. Similarly to our study, patients in these studies presented with baseline signs/symptoms of more severe grades compared to those in Ganz et al. study [21]. Overall, these data reemphasize the complexity of environmental studies performed in the domain of allergy, for which the major limitation remains the variance of exposure to allergens during the study period.

Topical anti-allergy agents such as ketotifen and olopatadine, which combine anti-histaminic and mast cell stabilizer actions, are nowadays favored for symptom relief of SAC [6]. Advantages of these dual-mechanism anti-allergic molecules include their rapid onset of action, triggered by immediate histamine receptor antagonism, and their additional

long-term effects on the mediators of the late-phase allergic reaction. Following the first instillation, itching relief was confirmed to be very fast as the major part of the treatment action on this symptom already took place within 3 minutes, with about two-third of the patients having no more severe to incapacitating itching in both groups. The rapidity and strength of both anti-allergic agents was corroborated by a decrease in overall ocular discomfort perceived by the patients, which was similar with both treatments. On a longer term, the main sign/symptoms of SAC already improved at day 7, and were absent in most patients at day 28. Only a non-significant trend in favour of ketotifen treatment was observed for conjunctival hyperaemia. The therapeutic efficacy of preservative-free ketotifen solution and olopatadine hydrochloride was confirmed by the relief of other SAC symptoms/signs, without differences between treatment groups. All patients experienced irritation/burning and stinging at baseline, while these symptoms improved for most of them in both treatment groups. At the end of the study, no chemosis was reported, and eyelid swelling and superficial punctate keratitis improved dramatically in both treatment groups. Safety was also similar with both treatments, while a trend for a better tolerability with relatively less ocular complains upon instillation (mainly irritation/burning/stinging) was reported in the Ketotifen group.

Increased expression of CAMs such as ICAM-1 on conjunctival surface cells is believed to explain the recruitment of inflammatory cells to the conjunctiva in patients with SAC. Improvements in the symptoms/signs of SAC were associated with a slight reduction in the expression level of ICAM-1 on conjunctival surface cells, with no statistically significant difference between ketotifen and olopatadine. Although confirmatory of the results by Avunduk and co-workers [7], a less pronounced effect of these two agents on ICAM-1 expression was observed in our study. It is likely that the weak level of ICAM-1 expression observed at inclusion

in our study might have prevented the detection of any significant impact of treatment. In particular, we cannot rule out that the slight trend in favour of ketotifen for reducing ICAM-1 expression, along with its effect on conjunctival hyperaemia, could be an advantage of the preservative-free formulation of ketotifen eye drops. However, in view of the low number of patients with interpretable results, definite conclusions regarding ICAM-1 expression analysis could not be drawn.

Conclusion

This 1-month study was designed to compare in clinical settings, preservative-free ketotifen fumarate 0.025% and olopatadine hydrochloride 0.1% eye drops. The ocular composite outcome showed a fast and similar clinical improvement of SAC symptoms/signs with both treatments. A trend in favour of ketotifen treatment was exhibited for conjunctival hyperaemia and overall tolerability assessed by the patients.

Disclosure of interest

D.R. and H.R. are employees of Laboratoires THEA. B.M. was the investigator coordinator of this study and received financial compensation from Laboratoires THEA. T.B., M.K., R.M. and D. B-G. were investigators of this study and received financial compensation from Laboratoires THEA. F. B-B declares that he has no conflicts of interest concerning this article.

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References

- [1] Leonardi A. Emerging drugs for ocular allergy. *Expert Opin Emerg Drugs* 2005;10:505–20.
- [2] Leonardi A. Pathophysiology of allergic conjunctivitis. *Acta Ophthalmol Scand Suppl* 1999;228:21–3.
- [3] Leonardi A. Role of histamine in allergic conjunctivitis. *Acta Ophthalmol Scand Suppl* 2000;230:18–21.
- [4] Bielory L, Ghafoor S. Histamine receptors and the conjunctiva. *Curr Opin Allergy Clin Immunol* 2005;5:437–40.
- [5] Choi SH, Bielory L. Late-phase reaction in ocular allergy. *Curr Opin Allergy Clin Immunol* 2008;8:438–44.
- [6] Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol* 2005;115:118–22.
- [7] Avunduk AM, Tekelioglu Y, Turk A, Akyol N. Comparison of the effects of ketotifen fumarate 0.025% and olopatadine HCl 0.1% ophthalmic solutions in seasonal allergic conjunctivitis: a 30-day, randomized, double-masked, artificial tear substitute-controlled trial. *Clin Ther* 2005;27:1392–402.
- [8] Leonardi A, Abelson MB. Double-masked, randomized, placebo-controlled clinical study of the mast cell-stabilizing effects of treatment with olopatadine in the conjunctival allergen challenge model in humans. *Clin Ther* 2003;25:2539–52.
- [9] Ciprandi G, Tosca MA, Cosentino C, Riccio AM, Passalacqua G, Canonica GW. Effects of fexofenadine and other antihistamines on components of the allergic response: adhesion molecules. *J Allergy Clin Immunol* 2003;112:578–82.
- [10] Leonardi A, DeFranchis G, De Paoli M, Fregona I, Plebani M, Secchi A. Histamine-induced cytokine production and ICAM-1 expression in human conjunctival fibroblasts. *Curr Eye Res* 2002;25:189–96.
- [11] Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs* 2005;65:215–28.
- [12] Lambiasi A, Micera A, Bonini S. Multiple action agents and the eye: do they really stabilize mast cells? *Curr Opin Allergy Clin Immunol* 2009;9:454–65.
- [13] Grant SM, Goa KL, Fitton A, Sorkin EM. Ketotifen. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma and allergic disorders. *Drugs* 1990;40:412–48.
- [14] Schoch C. Effects of ketotifen 0.025% and lodoxamide 0.1% on eosinophil infiltration into the guinea pig conjunctiva in a model of allergic conjunctivitis. *J Ocul Pharmacol Ther* 2003;19:153–9.
- [15] Abelson MB, Chapin MJ, Kapik BM, Shams NB. Efficacy of ketotifen fumarate 0.025% ophthalmic solution compared with placebo in the conjunctival allergen challenge model. *Arch Ophthalmol* 2003;121:626–30.
- [16] Crampton HJ. Comparison of ketotifen fumarate ophthalmic solution alone, desloratadine alone, and their combination for inhibition of the signs and symptoms of seasonal allergic rhinoconjunctivitis in the conjunctival allergen challenge model: a double-masked, placebo- and active-controlled trial. *Clin Ther* 2003;25:1975–87.
- [17] Kidd M, McKenzie SH, Steven I, Cooper C, Lanz R, Australian Ketotifen Study Group. Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *Br J Ophthalmol* 2003;87:1206–11.
- [18] Uchio E. Treatment of allergic conjunctivitis with olopatadine hydrochloride eye drops. *Clin Ophthalmol* 2008;2:525–31.
- [19] Borazan M, Karalezli A, Akova YA, Akman A, Kiyici H, Erbek SS. Efficacy of olopatadine HCl 0.1%, ketotifen fumarate 0.025%, epinastine HCl 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions for seasonal allergic conjunctivitis: a placebo-controlled environmental trial. *Acta Ophthalmol* 2009;87:549–54.
- [20] Berdy GJ, Spangler DL, Bensch G, Berdy SS, Brusatti RC. A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. *Clin Ther* 2000;22:826–33.
- [21] Ganz M, Koll E, Gausche J, Detjen P, Orfan N. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Ther* 2003;20:79–91.
- [22] Varguez-Rodriguez ME, Hernandez-Lopez A, Gomez-Davila Rde L. Comparison of olopatadin and ketotifen in the treatment of allergic conjunctivitis. *Rev Med Inst Mex Seguro Soc* 2009;47:399–404.
- [23] Brignole-Baudouin F, Ott AC, Warnet JM, Baudouin C. Flow cytometry in conjunctival impression cytology: a new tool for exploring ocular surface pathologies. *Exp Eye Res* 2004;78:473–81.
- [24] Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA* 2003;289:2554–9.