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Ophthalmic Lertal® spray for seasonal allergic conjunctivitis: an open-label clinical study

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Abstract

Introduction Seasonal allergic conjunctivitis (SAC) is estimated to affect 15 to 20% of people. Ophthalmic Lertal® spray (NTC S.r.l.) is a novel medical device developed for the management of SAC symptoms. This clinical study investigated the efficacy and safety of Lertal® spray in the treatment of SAC.

Methods Male and female patients aged 17 to 78 years with symptoms and a history of SAC were enrolled in this 4-week, open-label, single-arm, uncontrolled trial. Patients applied ophthalmic Lertal® spray three times daily. SAC symptoms were assessed by clinicians at study visits and by patients once weekly using the Total Ocular Symptom Score (TOSS) scale. The primary efficacy endpoint was the change in mean TOSS from baseline. Secondary efficacy endpoints included: change from baseline in individual ocular symptom scores; change from baseline in the daily use of anti-allergy medications; and patient assessment of how 'pleasant' the spray application felt.

Results Thirty patients (17 female and 13 male, mean age 43.4 years) were enrolled in this study. A 63% reduction in mean total symptom score was observed after 4 weeks of treatment (mean ± SD TOSS 10.0 ± 3.24 at visit 1 vs. 3.7 ± 2.25 at visit 2; $P<0.001$). All mean scores for the individual ocular symptoms were significantly reduced from baseline. In patients who continued to use anti-allergy medications (n=15) during the period of Lertal® administration, there was a significant ($P<0.001$) reduction in the mean overall daily use. No clinically relevant adverse effects were reported.

Conclusion Ophthalmic Lertal® spray effectively reduces ocular symptoms in patients with SAC and may allow for a reduction in the daily usage of anti-allergy medications.

Introduction

Seasonal allergic conjunctivitis (SAC) is caused by conjunctival inflammation in response to exposure to seasonal allergens (e.g. airborne pollens) [1-3]. Approximately 15–20% of people worldwide are thought to be affected by SAC or perennial allergic conjunctivitis, although estimates vary [3].

SAC results from IgE-mediated degranulation of sensitized mast cells in the conjunctiva, which increases the tear levels of histamine and other vasoactive substances (e.g. prostaglandins and leukotrienes) [1-3]. The release of inflammatory mediators triggers the signs and symptoms of SAC, including ocular itching, redness, tearing and photophobia, and increases activation and recruitment of inflammatory cells [1-3].

Pharmacological management of SAC often involves the topical and systemic use of decongestants, antihistamines (often in combination with decongestants or mast cell stabilizers) and corticosteroids; however, these agents provide only short-term relief from symptoms, and antihistamines and corticosteroids are associated with adverse effects [1, 4, 3, 5].

Ophthalmic Lertal® (NTC S.r.l.) spray is a novel medical device containing *Perilla frutescens* extract, hyaluronic acid and liposomes, and is being developed for the management of SAC symptoms. It has been demonstrated that *P. frutescens* extract, which is rich in rosmarinic acid, has anti-allergy activity in *in vitro* [6] and animal models [7, 6, 8-10]. Hyaluronic acid is a naturally occurring linear disaccharide polymer with lubricating and rehydrating properties commonly used in the management of dry eye syndrome [11]. Liposomal eye sprays may provide symptomatic relief for SAC, which often causes a tear film deficiency, by stabilizing the tear film lipid layer [12].

The aim of this open-label clinical study was to investigate the efficacy and safety of ophthalmic Lertal® spray for use in patients with SAC.

Methods

Patients

Males or females aged 15 to 78 years with symptoms of ocular seasonal allergic conjunctivitis (SAC) at baseline and a history of objectively diagnosed SAC for ≥1 year were enrolled in this study. Patients were positive for airborne allergens in a skin prick or radioallergosorbent test (or

equivalent). Concomitant use of anti-allergy medications (topical or systemic antihistamines or corticosteroids or topical decongestants) was permitted. Exclusion criteria included: women who were breastfeeding, pregnant or wishing to become pregnant during the study; patients with a bacterial or viral infection of the eye, paranasal sinuses, ear or upper or lower respiratory tracts within 30 days of enrolment; wearers of contact lenses; patients who were undergoing immunotherapy; and patients who had undergone refractive surgery and/or cataract surgery within 1 year of enrolment.

All study participants provided informed consent prior to their enrolment the study. This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 (revised 2013).

Study design

This was a 4-week, open-label, single-arm, uncontrolled trial. Patients were consecutively enrolled during the peak pollen season.

Patients applied Lertal® spray to the closed eyelid three times daily (morning, midday and evening); additional doses were applied as needed for acute SAC signs and symptoms.

Patients underwent two clinic visits; a baseline visit (Visit 1) and an end of study (EOS) visit (Visit 2; i.e. 4 weeks after starting study treatment). Ocular signs and symptoms were recorded using the Total Ocular Symptom Score (TOSS) scale (where 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms and 3 = severe symptoms) for the following nasal and ocular signs and symptoms: ocular itching, lacrimation, conjunctival congestion, ocular hyperemia and photophobia. Symptoms were assessed by clinicians at Visits 1 and 2.

Assessments

The primary efficacy endpoint was the change in mean TOSS (i.e. ocular signs/symptoms) from baseline after 4 weeks of study treatment.

Secondary efficacy endpoints included: change from baseline in individual ocular symptom scores; change from baseline in the daily use of anti-allergy medications; and patient assessment of how 'pleasant' the spray application felt.

For assessment of changes in concomitant use of anti-allergy medications, patients were divided into two groups: the first group continued taking anti-allergy medications as needed, and the second (with lower baseline usage due to less severe and disabling symptoms) were instructed to discontinue anti-allergy medications (rescue treatment was permitted).

Statistical analysis

Statistical analyses were conducted after the end of the study using G*Power, version 3.1.2, and the Student's paired t-test to determine the change in mean TOSS from baseline to EOS. Summary statistics (mean ± standard deviation) were presented for continuous variables. Statistical analysis of the primary endpoint was conducted with a two-tailed test, with a significance level of 5%.

It was estimated that a sample size of 23 patients would provide ~100% power to show a significant change from baseline in mean TOSS at EOS.

Results

The study enrolled 17 female and 13 male patients (mean [range] age of 43.4 [17–78] years) with symptoms of SAC and a history of SAC ≥1 year (Table 1); all 30 patients completed the study with good compliance.

Efficacy

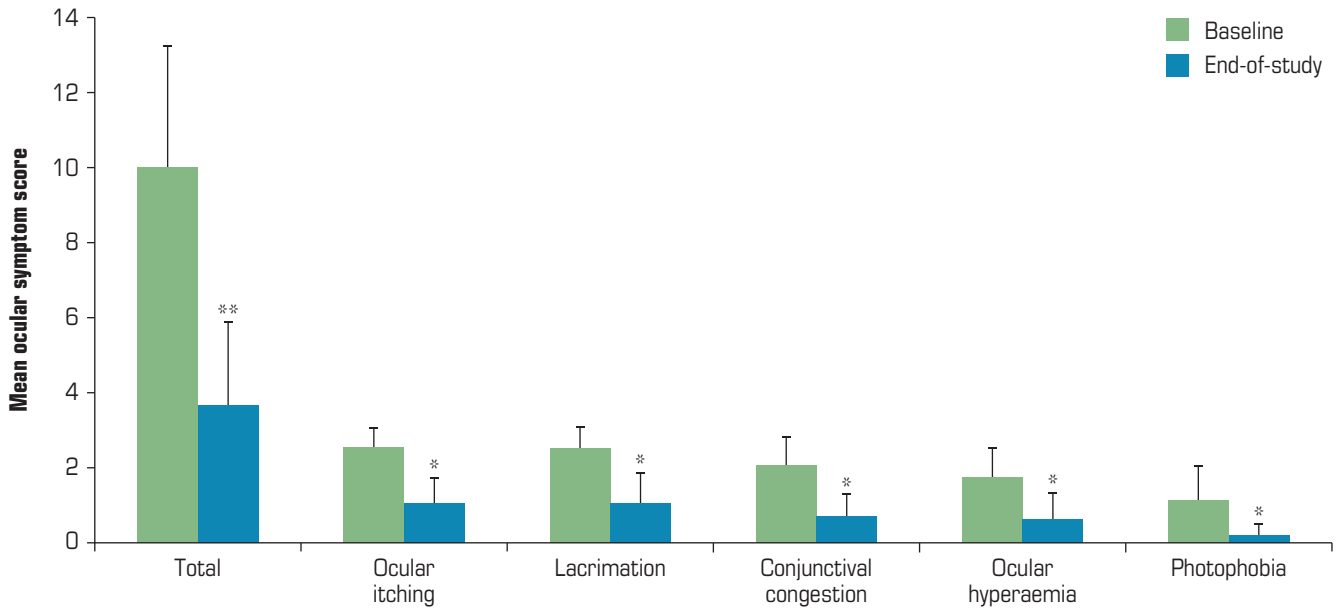
After 4 weeks of Lertal® spray administration, there was a significant reduction in all ocular signs and symptoms from baseline (mean ± SD TOSS 10.0 ± 3.24 at visit 1 vs. 3.7 ± 2.25 at visit 2; P<0.001) among patients with SAC (Figure 1), corresponding to a 63% reduction in mean total symptom score.

Mean scores for the individual ocular symptoms were all significantly reduced from baseline at EOS (Figure 1), with reductions from baseline in mean symptom scores of 56% for ocular itching, 58% for lacrimation, 63% for ocu-

Tabella 1. Demographic and baseline characteristics of the study population.

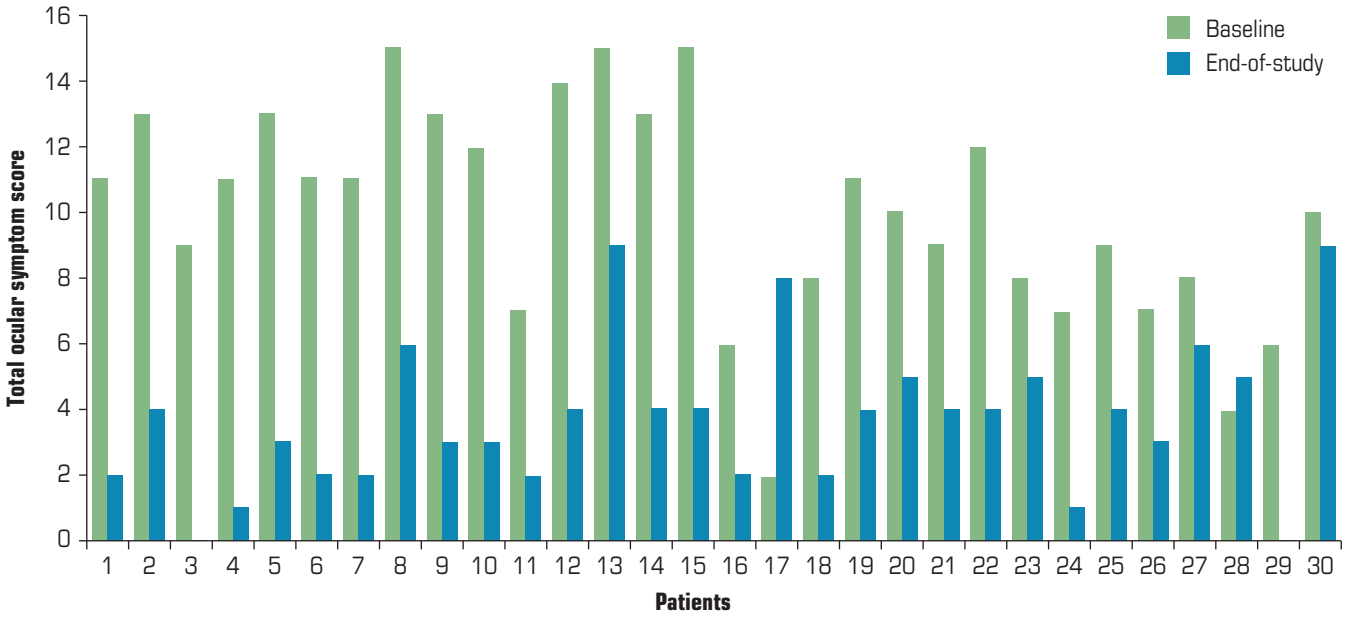
	N=30
Age, years (mean [range])	43.4 [17–78]
Sex, n (%)	
Male	13 (43.3)
Female	17 (56.7)
Duration of allergy, years (mean [range])	5.2 [1–20]
Time since last prick test, years (mean [range])	2.1 [1–6]
Main allergen, n (%)	
Birch	2 (6.7)
Cat fur	3 (10.0)
Grasses	2 (6.7)
Olive tree	2 (6.7)
Parietaria	21 (70.0)

Figure 1. Mean total and individual ocular symptom scores at baseline and end of study (after 4 weeks' treatment with Lertal® spray) in patients with seasonal allergic conjunctivitis (n=30).



Evaluation scale: 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms. *P<0.01, **P<0.001 vs. baseline.

Figure 2. Total ocular symptom scores at baseline and end of study (after 4 weeks' treatment with Lertal® spray) for individual patients with seasonal allergic conjunctivitis

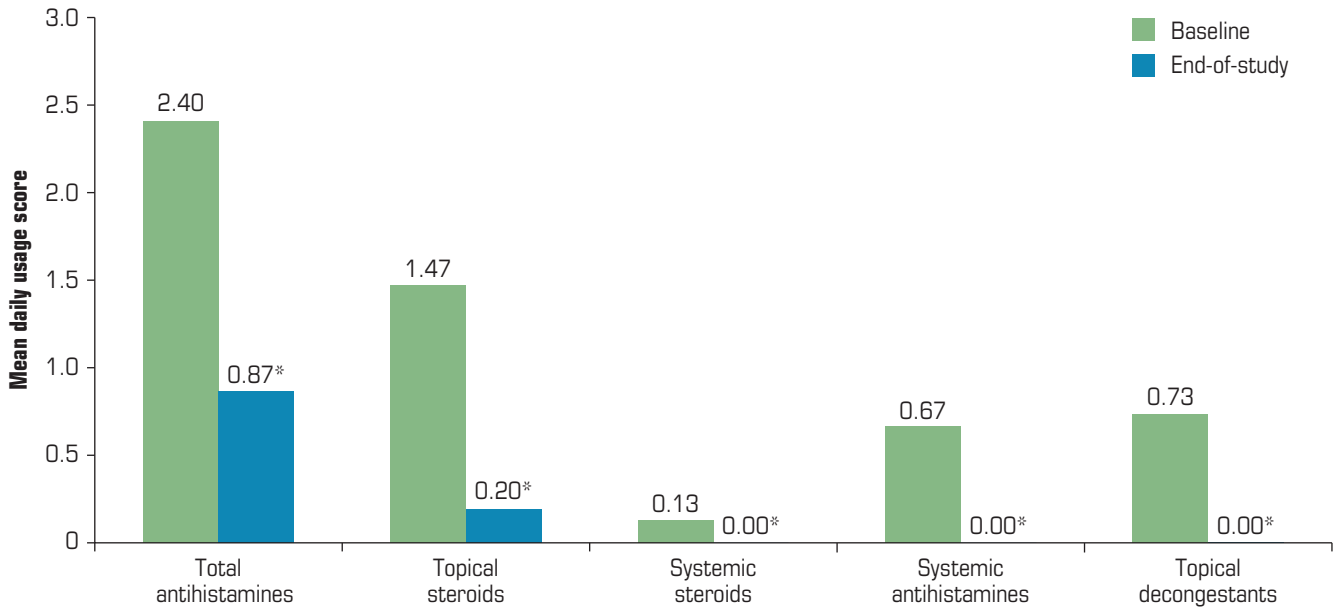


Evaluation scale: 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms.

lar hyperemia, 66% for conjunctival congestion and 85% for photophobia. With regard to changes in TOSS scores for individual patients, 27 patients (90%) showed improvements from baseline at EOS, while three patients (10%) were considered non-responders (Figure 2).

Among patients who continued concomitant use of anti-allergy medications (n=15) due to the severity of their symptoms at the beginning of the study, there was a significant (P<0.001) reduction in the mean overall daily use of all medications and of each individual drug class (Figure 3), with percentage reductions in mean daily usage scores of 64% to 100%.

Figure 3. Mean daily usage of anti-allergy medications at baseline and end of study (after 4 weeks' treatment with Lertal® spray) among a sub-group of patients with seasonal allergic conjunctivitis (n=15).



Daily usage scale: 0 = none; 1 = once daily; 2 = two or three times daily; 3 = more than three times daily. *P<0.001 vs. baseline.

In a subjective assessment of how pleasant the spray application felt, 55% of patients answered 'very pleasant', 30% answered 'pleasant' and 15% answered 'acceptable'. In particular, the majority of patients described a pleasant feeling of coolness in the ocular area and resolution of the itching a few minutes after the application of the spray.

Safety and tolerability

No adverse events were observed during the 2-hour period following Lertal® spray administration.

Overall, during 4 weeks' treatment, no clinically relevant adverse effects were reported.

Discussion

This study demonstrated that ophthalmic Lertal® spray is effective in reducing the ocular signs and symptoms of SAC. After 4 weeks' treatment with Lertal® spray, patients with SAC had a 63% mean reduction in ocular symptoms overall, and a subgroup of patients showed significant reductions in anti-allergy and decongestant medication use. During the study, all patients showed good treatment compliance with Lertal® spray.

The results of this study are consistent with previous clinical trials of *P. frutescens*-containing products. In a 21-day, randomized, double-blind, placebo-controlled trial in patients with seasonal allergic rhinoconjunctivitis, oral supplementation with *P. frutescens* extract significantly reduced total symptoms, itchy eyes, watery eyes and itchy nose [13]. In a 1-month, open-label, single-arm trial in patients with seasonal allergic rhinitis, orally administered Lertal® tablets (containing *P. frutescens*, the flavonoid quercetin and vitamin D_3) significantly reduced total and individual symptom scores [14].

Limitations of the current study include its small population size, open-label nature and lack of comparator group. Placebo- or active comparator-controlled studies in larger patient populations are warranted.

Conclusion

Ophthalmic Lertal® spray effectively reduces ocular symptoms in patients with SAC. The reduction of SAC symptoms with Lertal® spray may allow for a reduction in the daily usage of anti-allergy and decongestant medications in patients with SAC. Compared with these treatments ophthalmic Lertal® spray is a safe and convenient alternative. As such, it has the potential to reduce the use of anti-allergy and decongestant agents, and improve quality of life in patients with SAC.

Key points

Why carry out this study?

- Seasonal allergic conjunctivitis (SAC) affects approximately 15-20% of the world's population.
- Current treatments provide only short-term relief and cause significant side-effects.
- The aim of this study was to evaluate the efficacy and safety of ophthalmic Lertal® spray (NTC S.r.l.) in patients with SAC.

What was learned from the study?

- Ophthalmic Lertal® spray was effective in reducing ocular symptoms and well tolerated in patients with SAC.
- Ophthalmic Lertal® spray is a safe and convenient alternative to currently available treatments and has the potential to reduce the need for drug treatment and improve quality of life in patients with SAC.

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