

A randomized, double-masked, placebo-controlled parallel study of 0.2% loteprednol etabonate in patients with seasonal allergic conjunctivitis

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Background: Loteprednol etabonate is a site-active corticosteroid with efficacy and safety in treating ocular inflammation at the 0.5% concentration. Evidence from dose-response studies suggested that the 0.2% concentration might be effective in treating ocular allergy.

Objectives: The objective of this study was to evaluate the effects of 0.2% loteprednol etabonate in reducing the signs and symptoms of seasonal allergic conjunctivitis.

Methods: This was a randomized, double-masked, placebo-controlled, parallel-group multicenter study. Patients with signs and symptoms of environmental seasonal allergic conjunctivitis received either loteprednol etabonate or placebo bilaterally four times daily for 42 days.

Results: Enrolled were 133 patients (66 receiving loteprednol etabonate; 67 receiving placebo). A reduction in severity was seen in both loteprednol etabonate and placebo groups for bulbar conjunctival injection (1.3 vs 0.9 units on a 0 to 3 scale) and itching (3.5 vs 3.1 units on a 0 to 4 scale) over the first 2 weeks. The treatment effect was -0.5 and -0.6 units in favor of loteprednol etabonate ($P < .001$). Resolution (the proportion of patients with the sign or symptom no longer present) at visit 4 (day 14) strongly favored loteprednol etabonate-treated patients over placebo-treated patients (31% and 9%, and 54% and 38%, for injection and itching, respectively). Both treatments were well tolerated. No patients in either treatment group (0 for loteprednol etabonate and 0 for vehicle) had an elevation of intraocular pressure of 10 mm Hg or greater during the 6 weeks of treatment.

Conclusions: Loteprednol etabonate (0.2%) was more effective than placebo in the treatment of seasonal allergic conjunctivitis. Loteprednol etabonate (0.2%) had a safety profile comparable to placebo during this 6-week trial. (*J Allergy Clin Immunol* 1998;102:251-5.)

Key words: Loteprednol etabonate, seasonal allergic conjunctivitis, controlled clinical trial, ocular allergy

Seasonal allergic conjunctivitis represents an allergic reaction to certain pollens and is manifested by mild to severe symptoms of ocular itching, redness, epiphora, and secretions. The disease mechanism is primarily a type I hypersensitivity response. The disease is generally not sight-threatening, but it brings much discomfort associated with significant morbidity rates and loss of working time. From a clinical trial perspective, seasonal allergic conjunctivitis is highly prevalent and it is synchronized with pollen counts leading to predictive dates of morbidity and for the recruitment of patients in endemic areas.

Loteprednol etabonate is a novel corticosteroid designed to be active at its site of application and to undergo a rapid, predictable hydrolysis to an inactive metabolite.¹⁻³ At the 0.5% concentration, loteprednol etabonate was found effective and relatively safe in double-masked, controlled studies in several indications, including prophylaxis of seasonal allergic conjunctivitis,⁴ treatment of giant papillary conjunctivitis,^{5, 6} uveitis,⁷ and postoperative inflammation.⁸

Given the efficacy and safety profile of 0.5% loteprednol etabonate in the treatment of external inflammatory ocular conditions, consideration was given to the formulation of a lower concentration product designed specifically to optimize the safety and efficacy profile for the treatment of seasonal allergic conjunctivitis. In the conjunctival provocation test model,⁹ which is sensitive to corticosteroids,¹⁰ three concentrations of loteprednol etabonate (0.1%, 0.2%, and 0.3%) were evaluated, and the 0.2% concentration was chosen for further evaluation.¹¹

The objectives of this study were to evaluate the effectiveness of 0.2% loteprednol etabonate ophthalmic suspension (loteprednol etabonate) in reducing the ocular signs and symptoms of moderate to severe seasonal allergic conjunctivitis.

METHODS

Patients and methods

This was a prospective, double-masked, placebo-controlled, multicenter study. Enrolled in the study were adult patients with a history of positive skin prick or RAST, and at the time of enrollment, with moderate to severe signs and symptoms of seasonal allergic conjunctivitis caused by mountain cedar pollen [at least 4+ itching (0 to 4 scale) and 2+ redness (0 to 3 scale)]. Women of childbearing potential were required to be using adequate birth control and have a negative urinary pregnancy test at entry. Excluded from the study were patients with a

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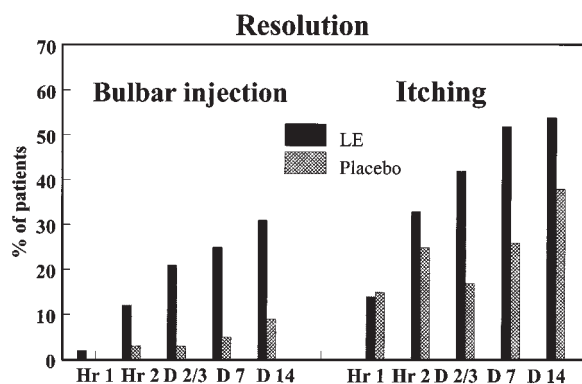


FIG. 1. Resolution for bulbar injection and itching. Resolution is defined as the proportion of patients with a 0 score. Sample size at baseline was 66 for loteprednol etabonate and 67 for placebo. Sample size at day 2/3 through day 14 varied by up to 3 per group. LE, Loteprednol etabonate.

history of allergic hypersensitivity to corticosteroids; recent use of a systemic or ocular corticosteroid, nonsteroidal anti-inflammatory agent or other anti-allergic agents, ocular hypertension or any type of glaucoma; recent intraocular or laser surgery; best corrected visual acuity of 20/100 or worse in either eye; ocular pathology other than acute, seasonal allergic conjunctivitis or systemic allergic disorders such as asthma or rhinitis; and contact lens wear during the course of the study.

On the day of enrollment, signs and symptoms of allergic conjunctivitis were evaluated at baseline. Qualified patients were randomized to receive either double-masked 0.2% loteprednol etabonate ophthalmic suspension or placebo, bilaterally. At 1 and 2 hours (± 10 minutes) after the first medication drop, an ocular examination for signs and symptoms was carried out. The patients were instructed to begin dosing every 4 hours while awake (approximately 8 AM, noon, 4 PM, and 8 PM). Patients were asked to return on days 2 or 3, 7, 14, 28, and 42 (visits 2 to 6, respectively) for evaluation and at approximately the same time as on visit 1.

Ocular safety evaluations included an external examination, slit lamp examination, applanation tonometry, and visual acuity taken before enrollment and at the scheduled visits during the study.

The study was designed to have a fixed number of visits over 6 weeks, and by virtue of this design, some patients continued treatment beyond the end of the pollen season. However, the primary focus for efficacy was the first 14 days of treatment. The primary efficacy variables were bulbar conjunctival injection (sign) and ocular itching (symptom). An Investigator Global Assessment of the Control of Signs and Symptoms of seasonal allergic conjunctivitis was recorded beginning at visit 3 (day 7). Investigators were required to record local environmental pollen counts.

This study was reviewed by governing Institutional Review Boards, and all patients provided written informed consent. The study was carried out during the mountain cedar pollen season in South Central Texas (December 1995 to February 1996).

Statistical evaluation

For the efficacy analysis of signs and symptoms, the mean for the right and left eyes was calculated for each patient at each visit.¹² An intent-to-treat analysis was performed on all randomized patients with at least 1 follow-up evaluation after baseline, with last observation being carried forward for patients discontinuing before week 6 (visit 6). If the allergy season was considered to be over before visit 6 as judged by pollen counts ($<100/\text{m}^3$), then only visits during the season were to be included in the evaluation

of visits 5 and 6. For signs and symptoms, the comparability of the treatment groups was tested by using the Cochran-Mantel-Haenszel test for the equality of group mean ranks controlling for investigator. Comparability of investigators at baseline was tested by using the same analysis without stratification. The primary efficacy analysis was a repeated-measures analysis of covariance (baseline severity) with interaction on change from baseline at visits 2, 3, and 4, under the assumption of compound symmetry. The overall treatment effect (loteprednol etabonate – placebo) was estimated and its 95% confidence limits were provided; negative effects indicate that loteprednol etabonate is favored over placebo. A supportive univariate analysis for individual visit results was analyzed for equality of treatment group mean ranks with the use of the Cochran-Mantel-Haenszel test controlling for investigator. The sample size at visit 6 precluded meaningful statistical analysis. Analysis of Investigator Global Assessment was performed with the use of the Cochran-Mantel-Haenszel test controlling for investigator. The primary planned analysis of intraocular pressure was the relative incidence of elevations of 10 mm Hg or more from baseline.¹³ This study had at least 80% power to detect a difference between treatments of 0.5 standard deviation units at the 5% level of significance (two-tailed test).

RESULTS

One hundred thirty-three patients were enrolled in this study; 66 were assigned to receive loteprednol etabonate and 67 were assigned to receive placebo. One hundred twenty-six patients completed treatment through week 6. Dropped from the study were four patients (two in each treatment group) because of a medical event, a placebo-treated patient lost to follow-up, and two placebo-treated patients for administrative reasons. Because of low pollen levels, only 53 and 16 patients were considered for efficacy at 4 and 6 weeks.

There were no statistically significant differences between treatments in age (mean 41 to 42 years), sex (50% to 52% women), race (61% to 64% Caucasian and 28% to 33% Hispanic), iris color, or baseline pollen counts (approximately $11,000/\text{m}^3$; $P \geq .223$). There was no statistically significant difference at study entry between treatments for bulbar conjunctival injection ($P = .268$). All patients had +4 itching at entry.

For the primary sign, bulbar injection, during the primary evaluation (first 2 weeks), improvement was seen in both treatment groups (Table I). The estimated overall change from baseline for loteprednol etabonate was -1.32 units compared with -0.79 units for placebo for an estimated treatment effect (loteprednol etabonate – placebo) of -0.54 units. Treatment group ($P < .001$), baseline severity ($P < .001$), and investigator ($P < .001$) were all significant between-subject effects in the repeated-measures analysis of change from baseline. Loteprednol etabonate was also favored over placebo in resolution at day 14 (the proportion of patients with a 0 score), with the resolution for the loteprednol etabonate and placebo groups being 31% and 9%, respectively (Fig. 1).

For the primary symptom, itching, at the primary evaluation (first 2 weeks), improvement was also seen in both groups (Table II). The estimated overall change from baseline for loteprednol etabonate was -3.36 units compared with -2.75 units for placebo for an estimated treat-

TABLE I. Bulbar conjunctival injection

	Loteprednol etabonate	Placebo	Treatment effect*	
			Median	P value
Baseline				
<i>n</i>	66	67		
Mean	2.1	2.1	0.0	.268
SEM	0.0	0.0		
Change from baseline at:				
First 2 hours: estimated mean	−0.78	−0.38	−0.40†	<.001
First 2 weeks: estimated mean	−1.32	−0.79	−0.54†	<.001
Hour 1				
<i>n</i>	66	67		
Mean	−0.5	−0.3	0.0	.274
SEM	0.1	0.1		
Hour 2				
<i>n</i>	66	67		
Mean	−0.9	−0.4	−0.5	<.001
SEM	0.1	0.1		
Day 2-3				
<i>n</i>	66	65		
Mean	−1.1	−0.7	−0.5	.001
SEM	0.1	0.1		
Day 7				
<i>n</i>	65	65		
Mean	−1.3	−0.7	−0.5	<.001
SEM	0.1	0.1		
Day 14				
<i>n</i>	65	64		
Mean	−1.3	−0.9	−0.5	.006
SEM	0.1	0.1		
Day 28				
<i>n</i>	27	26		
Mean	−1.2	−0.7	−0.5	.030
SEM	0.1	0.1		
Day 42				
<i>n</i>	8	8		
Mean	−0.9	−0.5	0.0	.135
SEM	0.2	0.2		

Scale: 0 (none) to 3 (severe).

One placebo-treated patient did not have a valid on-treatment evaluation and was thus excluded from the intent-to-treat efficacy analysis for both injection and itching.

*Treatment effect is the large sample estimate of the median difference between treatment groups. Probability value is from Cochran-Mantel-Haenszel test for equality of treatment mean ranks, controlling for investigator.

†Repeated-measures analysis of covariance.

ment effect (loteprednol etabonate – placebo) of −0.62 units. Treatment group ($P < .001$), investigator ($P = .042$), and their interaction ($P = .026$) were significant between-subject effects in the repeated-measures analysis of change from baseline. Loteprednol etabonate was also favored over placebo for resolution at day 14, with the resolution for the loteprednol etabonate and placebo groups being 54% and 38%, respectively (Fig. 1).

At 2 weeks, the proportion of patients judged “mostly” to “fully” controlled in Investigator Global Assessment was 79% (52 of 66) for loteprednol etabonate and 47% (30 of 65) for placebo, with a median treatment effect of −1.0 units (in favor of loteprednol etabonate; $P < .001$).

Mean intraocular pressure at study entry was 14.6 and 14.4 mm Hg for the loteprednol etabonate and placebo,

respectively. No patients in either treatment group had an intraocular pressure elevation of 10 mm Hg or greater. The proportion of patients with at least one symptom was significantly higher in the placebo group (90%) than in the loteprednol etabonate group (68%, $P = .002$). This may be related to the signs and symptoms of seasonal allergic conjunctivitis in the placebo group being reported as medical events, as evidenced by the greater incidence for the placebo group for ocular and nasal symptoms (eg, discharge, epiphora, injection, and itching). The only symptom for which the incidence was significantly higher in the loteprednol etabonate group than in the placebo group was flu symptoms. Other than these events, there were few treatment differences of note and few events in either treatment group that were judged as related to therapy.

TABLE II. Itching

	Loteprednol etabonate	Placebo	Treatment effect*	
			Median	P value
Baseline				
<i>n</i>	66	67		
Mean	4.0	4.0		NA
SEM	0.0	0.0		
Change from baseline at:				
First 2 hours: estimated mean	-2.81	-2.78	-0.02†	.861
First 2 weeks: estimated mean	-3.36	-2.75	-0.62†	<.001
Hour 1				
<i>n</i>	66	67		
Mean	-2.6	-2.6	0.0	.590
SEM	0.1	0.1		
Hour 2				
<i>n</i>	66	67		
Mean	-3.1	-3.0	0.0	.304
SEM	0.1	0.1		
Day 2-3				
<i>n</i>	66	65		
Mean	-3.2	-2.6	-1.0	<.001
SEM	0.1	0.1		
Day 7				
<i>n</i>	65	65		
Mean	-3.4	-2.7	0.0	<.001
SEM	0.1	0.1		
Day 14				
<i>n</i>	65	64		
Mean	-3.5	-3.1	0.0	.034
SEM	0.1	0.1		
Day 28				
<i>n</i>	27	26		
Mean	-3.6	-3.4	0.0	1.000
SEM	0.2	0.2		
Day 42				
<i>n</i>	8	8		
Mean	-3.8	-4.0	0.0	.134
SEM	0.2	0.0		

Scale: 0 (none) to 4 (severe).

*Treatment effect is the large sample estimate of the median difference between treatment groups. Probability value is from Cochran-Mantel-Haenszel test for equality of treatment mean ranks, controlling for investigator.

†Repeated-measures analysis of covariance.

The two patients receiving placebo terminated from further study participation because of adverse events of severe itching and viral conjunctivitis. The two patients taking loteprednol etabonate were dropped for acute pharyngeal reaction with a headache and for elevated intraocular pressure 9 mm Hg above prestudy baseline at week 1.

DISCUSSION

Loteprednol etabonate (0.2%) was significantly more effective than its vehicle in the primary analysis of the primary signs and symptoms of seasonal allergic conjunctivitis as well as in a host of secondary and supportive analyses of primary, secondary, and supportive outcome measures (eg, discomfort, foreign body sensation, burning/stinging, photophobia, and palpebral conjunctival injection, chemosis, and erythema). These results were consistent in direction and magnitude with those in

a report of prophylactic use of 0.5% loteprednol etabonate in seasonal allergic conjunctivitis.⁴

There was substantial improvement in the patients receiving placebo, especially in the first few hours after treatment. One should consider that in this initial period, the patients were removed from their environmental challenge and were inside temperature-controlled offices. Frequent application of a vehicle with demulcent effects and frequent rinsing of the conjunctiva (dosing four times daily) may have effects of their own. However, because loteprednol etabonate-treated patients experienced even greater improvement, this suggests a substantial therapeutic effect beyond merely the vehicle and environmental control.

A concern with use of a corticosteroid in the treatment of allergy is the development of increases in intraocular pressure. In the present study with 6-week treatment, there were no clinically significant elevations in intraoc-

ular pressure as defined a priori (≥ 10 mm Hg).¹³ In a separate study in corticosteroid responders, loteprednol etabonate had a very low incidence of intraocular pressure elevation relative to prednisolone acetate.¹⁴

There were no serious or unexpected adverse effects; other ocular adverse events were consistent with a diagnosis of allergic conjunctivitis,¹⁵ and the nonocular adverse events were consistent with allergies (eg, rhinitis) or were of the type frequently reported in controlled clinical trials (eg, headache).^{16, 17}

In summary, 0.2% loteprednol etabonate provided clinically and statistically significant improvement in the treatment of seasonal allergic conjunctivitis in well-controlled clinical studies. Given its safety profile, especially with respect to intraocular pressure, it may prove useful in the treatment of seasonal allergic conjunctivitis.

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