

Letter to the Editor

Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study

To the Editor:

Vernal keratoconjunctivitis (VKC) is a severe allergic disease that affects the pediatric population. Treatment involves topical antiallergic agents, which are effective in patients with mild disease, whereas most patients with severe disease require some topical steroid therapy. The remarkable recovery with steroids tempts the caretaker to overuse these drugs, and the chronicity of this disease demands strict surveillance against steroid abuse, which inevitably leads to side effects, such as cataracts and glaucoma.¹⁻⁴ The physician's primary objective with the patient with VKC is to prevent and minimize acute flare-ups, as well as to treat them when they do occur with the safest therapy available. A major risk factor for a worse visual outcome is a higher number and severity of recurrences, as well as longer disease duration.^{1-3,5}

In this double-masked, randomized, controlled, crossover 2-year study, we investigated the efficacy and safety of 0.05% topical cyclosporine in patients with VKC (see Fig E1 in this article's Online Repository at www.jacionline.org). To further define what role this drug can play in VKC, the primary outcome evaluated was the ability of 0.05% cyclosporine to prevent flare-ups. Additionally, the efficacy of a higher dose, 0.1%, was compared with that of 0.15% dexamethasone during acute relapses in a nested, double-masked, randomized, controlled subgroup. The methods are detailed in the Methods section in this article's Online Repository at www.jacionline.org.

Thirty-four patients with nonactive VKC were included (30 male and 4 female patients; mean age, 14 ± 7 years). Clinical characteristics of the patient population are shown in Table E1 in this article's Online Repository at www.jacionline.org.

During the 2-year period, 48 recurrences were observed. Fewer than half of the patients in the cyclosporine group had recurrences (10/31 patients; $n = 15$ recurrences, 0.48 ± 0.89 mean recurrences per patient per year) compared with the ketotifen group (18/33 patients; $n = 33$, 1 ± 1.09 recurrences per patient per year; $P = .0371$; see Fig E2, A, in this article's Online Repository at www.jacionline.org).

In the 2-year analysis, logistic regression showed that patients treated with ketotifen had a risk of recurrence 2.4 times higher than that of patients treated with cyclosporine (odds ratio, 2.44; 95% CI, 1.08-5.48; $P = .031$). Survival analysis showed that the cyclosporine group remained recurrence free for a significantly longer period of time than the ketotifen group ($P < .05$; see Fig E2, B). The smoothing hazard estimate determined that during the 6-month treatment period, risk of recurrence was higher in the ketotifen group (11%) than in the cyclosporine group (4%) immediately after an episode (see Fig E2, C, in this article's Online Repository at www.jacionline.org).

Analyses of secondary outcomes demonstrated that cyclosporine significantly improved itching ($P = .02$), photophobia ($P = .04$), and hyperemia ($P = .04$) compared with ketotifen (see Fig E3 in this article's Online Repository at www.jacionline.org). No other significant differences were noted (see Table E2 in this article's Online Repository at www.jacionline.org). No

significant differences in primary and secondary outcomes were noted between atopic and nonatopic patients, positive and negative skin test responders, and monosensitized and polysensitized patients. No significant differences were reported in the air allergen concentrations in Italy during the 2 years of the study (www.pollenallergia.net).

During cyclosporine treatment, 2 adverse events were observed: 1 patient presented with onset of a pterygium, and another had urticaria. These adverse events were determined to be possibly related to drug treatment. There were no statistical differences in adverse event or termination/discontinuation rates between the 2 groups. Both drugs were well tolerated.

All patients with a precisely defined, clinically significant recurrence of ocular inflammation during treatment were included in the nested study. Results showed that 23 (48%) of 48 recurrences required a second week of open-label 0.15% dexamethasone 4 times daily as rescue medication: 16 in the 0.1% cyclosporine group and 7 in the dexamethasone group. This difference was statistically significant ($P = .020$, see Fig E4 in this article's Online Repository at www.jacionline.org). Secondary analyses of signs and symptoms demonstrated the superiority of dexamethasone with respect to cyclosporine in treating hyperemia ($P = .0003$), itching ($P < .0001$), photophobia ($P < .0001$), secretion ($P = .03$), tearing ($P = .04$), redness ($P < .0001$), mucous discharge ($P = .015$), corneal epitheliopathy ($P = .021$), fluorescein staining ($P = .0008$), total signs ($P = .0013$), and total symptoms ($P < .0001$, see Table E3 in this article's Online Repository at www.jacionline.org).

We demonstrated in patients with VKC that long-term treatment twice daily with 0.05% cyclosporine eye drops significantly reduced the number of recurrences of ocular allergic inflammation, events that are known to be closely related with a worse prognosis and visual outcome, compared with topical antiallergic treatment with 0.025% ketotifen fumarate.

Recurrences of VKC are characterized by severe conjunctival inflammation, often with corneal involvement that leads to neovascularization, scarring, irregular astigmatism, and permanent visual impairment in 6% to 12% of patients.^{1-3,5,6} Using the number of recurrences as the primary outcome in a VKC clinical trial should lead to a more accurate evaluation of a drug's ability to prevent permanent visual effects of this chronically cyclical disease in the long-term management of pediatric patients. In fact, as in all allergic diseases, signs and symptoms have great intrasubject and intersubject variability, even in the same day, because of exogenous factors, such as differences in pollen count, weather, and time spent outdoors, and to endogenous factors, such as varying allergic sensitivity and immune response. These variables render it extremely difficult to prove efficacy of a drug for long-term treatment in seasonal trials with pre-established time points.^{1,7}

In this study no significant difference in the total number of flare-ups between the first and second years were noted; however, we observed a marked reduction in the number of flare-ups in the cyclosporine-treated group during the second year of the study. Because no significant differences were reported in airborne allergen concentrations in Italy during the study, we can exclude that environmental triggers played a major role in the results of the crossover year. The difference in the number of flare-ups

during the second year of the study might have been due to the crossover design. In fact, we observed a marked difference in the dropout rate between the 2 experimental treatments during the first year. In line with this hypothesis, 4 patients dropped out for inefficacy in the ketotifen group during the second year.

In this study 0.05% cyclosporine significantly ameliorated the signs and symptoms of allergy (ie, itching, photophobia, and hyperemia) but was equivalent to ketotifen in controlling other secondary signs and symptoms. The composite sum scores were not significantly different. The only other comparable randomized clinical trial that investigated the efficacy of 0.5% cyclosporine eye drops versus an antiallergic agent, 0.5% ketorolac tromethamine, did not report significant differences in controlling the signs and symptoms of VKC.^{1,8}

The most clinically relevant finding of this study involved the results obtained with long-term, daily preventative treatment with a low concentration of cyclosporine and how this significantly affected the course of VKC, demonstrating it to be a valid steroid-sparing therapy. The results of the nested study demonstrated an inferior efficacy of the higher 0.1% cyclosporine dose compared with 0.15% dexamethasone. Steroid use led to a greater reduction in signs and symptoms, as well as a significantly lower number of patients (30%) requiring a second week of open-label rescue therapy than cyclosporine (64%). Cyclosporine was safe and well tolerated, confirming data from a recent study reporting no side effects in 594 patients with VKC or atopic keratoconjunctivitis treated with 0.1% cyclosporine for 1 year.⁹

In conclusion, in this randomized controlled study we report the safety and efficacy of topical 0.05% cyclosporine for the long-term prevention of VKC relapses. This finding is relevant to the long-term management of pediatric patients at risk of visual impairment, whether because of steroid abuse or continued recurrences of acute inflammation.

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Supported by an Italian Agency for Drug Administration (AIFA-Agenzia Italiana del Farmaco) grant.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

1. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology* 2000;107:1157-63.
2. Leonardi A. Vernal keratoconjunctivitis. pathogenesis and treatment. *Prog Retin Eye Res* 2002;21:319-39.
3. Tabbara KF. Ocular complications of vernal keratoconjunctivitis. *Can J Ophthalmol* 1999;34:88-92.
4. Fraunfelder FW. Corneal toxicity from topical ocular and systemic medications. *Cornea* 2006;25:1133-8.
5. Sacchetti M, Lambiase A, Mantelli F, Deligianni V, Leonardi A, Bonini S. Tailored approach to the treatment of vernal keratoconjunctivitis. *Ophthalmology* 2010;117:1294-9.
6. Cameron JA, Mullaney PB. Amblyopia resulting from shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. *J Pediatr Ophthalmol Strabismus* 1997;34:261-2.
7. Bonini S, Schiavone M, Centofanti M, Allansmith MR, Bucci MG. Conjunctival hyperresponsiveness to ocular histamine challenge in patients with vernal conjunctivitis. *J Allergy Clin Immunol* 1992;89:103-7.
8. Kosirukwongs P, Luengchaichawange C. Topical cyclosporine 0.5 per cent and preservative-free ketorolac tromethamine 0.5 per cent in vernal keratoconjunctivitis. *J Med Assoc Thai* 2004;87:190-7.
9. Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J, et al. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2009;25:365-72.

doi:10.1016/j.jaci.2011.07.004

METHODS

Patients and study design

This study was approved and funded by the Italian Agency for Drug Administration (AIFA-Agenzia Italiana del Farmaco) to support independent drug research for the National Health System.

It was performed in 2 Italian centers between March 2006 and November 2008. The study protocol was approved by both the Agenzia Italiana del Farmaco and by local ethics committees. Written informed consent for participation was obtained from parents according to local requirements.

Patients with VKC were screened for enrollment. They were eligible for randomization if they were given a diagnosis of VKC (ie, if they had a positive clinical history of allergic diseases and a history of recurrences of conjunctival inflammation with itching, conjunctival tarsal and/or limbal papillae, and the presence of eosinophils in conjunctival scrapings). Patients in the active phase of VKC (itching and/or conjunctival hyperemia scores >2) at the time of screening, the baseline examination, or both were excluded. Other exclusion criteria were contact lens wear, the presence of any other ocular disease, use of any other ophthalmic or systemic therapy, a history of ocular surgery in the preceding 6 months, and pregnancy or breast-feeding. No age and sex limits were defined. This study was registered at <http://clinicaltrials.gov> on January 2007 (registration no. NCT00426023).

Randomization and masking

Patients were randomly assigned in a 1:1 ratio to 0.05% cyclosporine cationic emulsion (NOVA22007; Novagali Pharma, Evry, France) or 0.025% ketotifen fumarate ophthalmic solution (Zaditen; Novartis, Siena, Italy).

Randomization was centralized and stratified by study site. The Biostatistics Department at the Campus Bio-Medico, University of Rome, generated a computerized randomization schedule. Experimental drugs were packaged into identical boxes containing 30 single-use vials. The study drug boxes were labeled with random 6-digit kit numbers. Patients, care providers, and investigators were all unaware of the allocation of the study drug. When all patients had completed the study, at the end of the 2-year study period, the randomization code was broken, and treatment groups were revealed.

Study intervention

All 34 subjects initiated treatment at the beginning of the spring season in March 2007. After a 2-week washout period, during which only preservative-free artificial tears were allowed, patients were treated in a double-masked fashion with either 0.05% cyclosporine or 0.025% ketotifen fumarate eye drops 2 times daily for a 6-month period commencing before the allergy season (March) and then running through it. In the following 6-month period, patients were only allowed to use preservative-free artificial tears. The crossover period was initiated in March 2008, the second year of the study, and patients were switched to the comparative treatment for the following 6 months in a double-masked fashion (Fig E1).

A thorough ocular and systemic clinical history was recorded. Patients were evaluated at baseline, after 4 and 12 weeks of treatment, at the end of treatment (6 months), and 4 weeks after treatment discontinuation for each year of the study. Additional examinations were scheduled at the patients' request in the case of disease recurrence. At each visit, signs and symptoms and fluorescein staining were evaluated, as well as uncorrected and best-corrected visual acuity, intraocular pressure with Goldman tonometry, and the results of an ocular fundus examination. Digital photographs were taken for documentation.

Primary and secondary outcomes

The primary outcome of the study was the number of recurrences of ocular surface inflammation in the 2 groups during the 6-month treatment period. We defined a clinically significant recurrence as at least a 100% increase in the sum of hyperemia, itching, Trantas dots, and the Oxford fluorescein and corneal epitheliopathy scores compared with the previous visit.

Secondary outcomes were (1) symptoms of itching, photophobia, redness, tearing, secretion, and blurry vision (graded as 0 = absent, 1 = mild, 2 = moderate, and 3 = severe); (2) the total symptoms score, which was the sum of the symptoms score from 0 to 18; (3) signs of conjunctival hyperemia, mucous discharge, tarsal and/or limbal papillae, Trantas dots, conjunctival fibrosis, corneal epitheliopathy, and corneal vessels graded from 0 to 3; (4) the total signs score, which was the sum of the signs scores from 0 to 24; and (5) corneal fluorescein staining graded according to the Oxford scheme from 0 to 5.

The safety end points included adverse events, compliance with treatment, drug tolerability, and dropout rate. Primary and secondary outcomes were evaluated and compared at each time point.

Nested study: Treatment of VKC recurrences

All subjects who manifested a precisely defined recurrence of ocular surface inflammation were included in the nested study. The aim of this study was to evaluate the efficacy of a higher 0.1% concentration of cyclosporine (NOVA22007, Novagali Pharma) compared with 0.15% dexamethasone eye drops (Etacortilen; SIFI, Lavinaio, Italy) for the treatment of the active phase of VKC.

When patients with recurrences were included in the nested study, they discontinued the preventative treatment and were randomized in a 1:1 ratio in a double-masked fashion to receive 0.1% cyclosporine or dexamethasone eye drops 4 times daily for 1 week.

Randomization was carried out as in the primary study. Experimental drugs were provided in identical boxes labeled with random 6-digit kit numbers that contained 30 single-use masked vials.

Patients were evaluated at baseline and after 3 and 7 days of treatment. Symptoms, signs, corneal fluorescein staining (Oxford scheme), uncorrected and best-corrected visual acuity, and intraocular pressure were evaluated as described above. If clinical signs and symptoms improved after 1 week of treatment, defined as a minimum 100% reduction of the sum of itching, conjunctival hyperemia, Trantas dots, corneal ulcer, and Oxford fluorescein scores with respect to baseline values, patients reinitiated the original masked preventative treatment (0.05% cyclosporine or ketotifen). Conversely, if symptoms did not improve, an open-label rescue treatment with 0.15% dexamethasone eye drops 4 times daily for 1 week was allowed. If the rescue medication proved ineffective in reducing signs and symptoms, the patient was terminated from the study.

The primary outcome of the nested study was the number of patients in each group who required the additional second, open-label rescue treatment with dexamethasone. The secondary outcomes were individual symptom (itching, photophobia, redness, tearing, secretion, and blurred vision) and sign (conjunctival hyperemia, mucous discharge, tarsal and/or limbal papillae, Trantas dots, conjunctival fibrosis, corneal epitheliopathy, and corneal vessels) scores, total symptoms and total signs scores, and the Oxford score. Safety end points included adverse events, compliance to treatment, drug tolerability, and dropout rate.

Statistical analysis

Sample size was calculated by defining the primary outcome as a 50% reduction in the number of recurrences in the cyclosporine group versus the ketotifen group (0.4 ± 0.5 vs 0.8 ± 0.5 recurrences per year per patient). A sample size of 26 patients with VKC was considered sufficient to detect significant differences in the primary outcome with 80% power for a type I error of 5%. Considering an estimated 25% dropout rate, 34 patients were required.

All data were entered into a database and analyzed with SPSS software (version 16; SPSS Institute, Inc, Chicago, Ill) at the Biostatistic Department at the Campus Bio-Medico of the University of Rome.

Without breaking the randomization code, an interim analysis was performed on the 2 masked groups at the end of the first year of treatment to identify any significant differences in recurrence rate and safety end points.

An intention-to-treat analysis was performed at the end of the 2-year study according to the protocol. The primary outcome was analyzed by using the Wilcoxon signed-rank test considering the difference between the number of

recurrences during treatment with cyclosporine and ketotifen. Additionally, the smoothed hazard estimate and the Kaplan-Meier survival estimate were performed to evaluate the risk of recurrence and the recurrence-free time in the 2 treatment groups.

Secondary outcomes were analyzed by considering the differences between all parameters evaluated during the 2 treatment periods. Repeated-measures

ANOVA was used to analyze secondary outcomes and clinical and safety parameters (adverse events and dropout rate).

For the nested study, the χ^2 test was performed to analyze the primary outcome: the number of patients requiring rescue medication in the cyclosporine versus the dexamethasone group. Data were expressed as means $\pm$ SDs, and a *P* value of less than .05 was considered statistically significant.

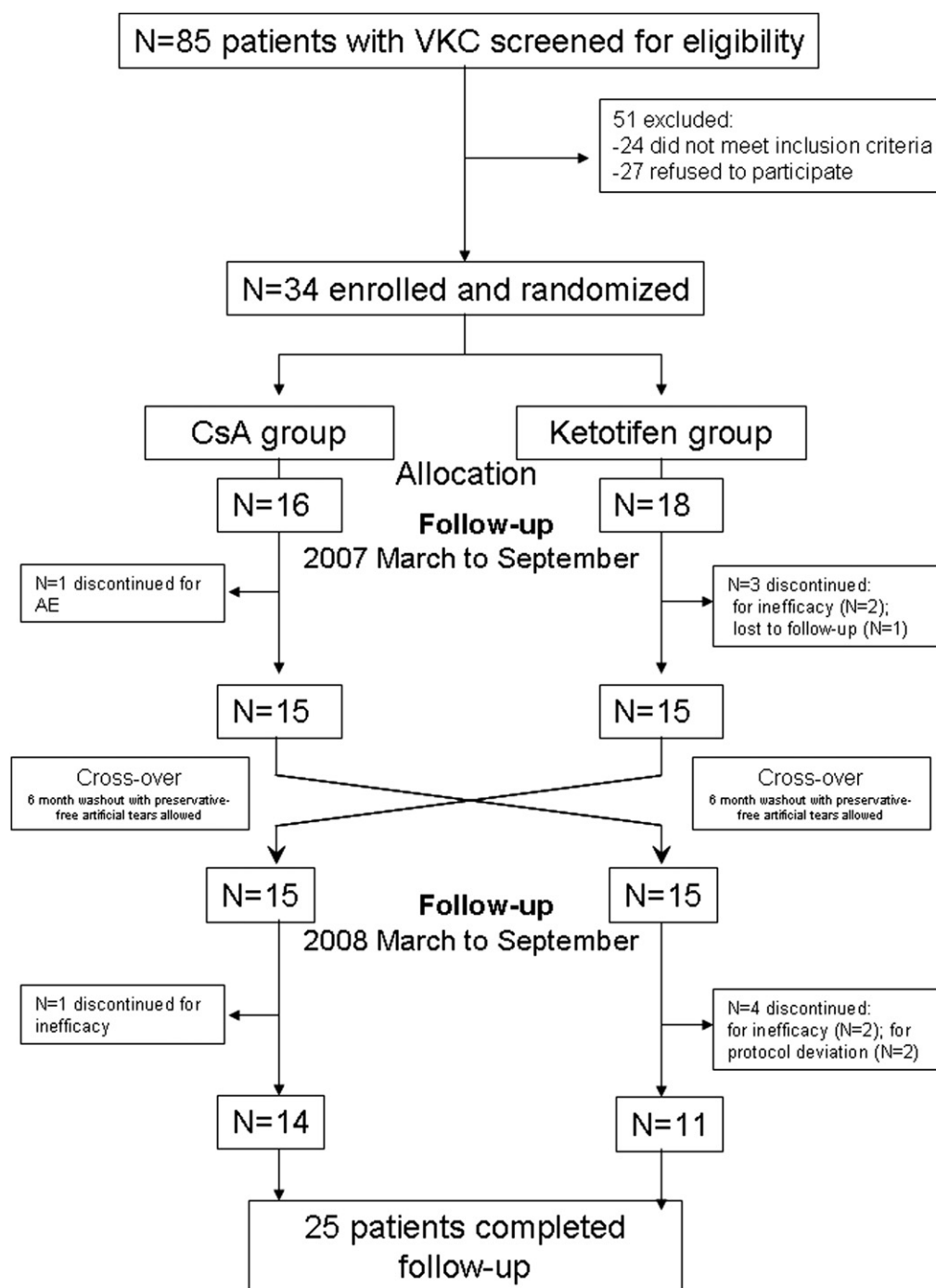


FIG E1. Study design. AE, Adverse event; CsA, cyclosporine.

A

Treatment sequence	CsA group		Ketotifen group		CsA-Ketotifen	
	Patients(N)	Recurrences (mean±SD)	Patients(N)	Recurrences (mean±SD)	Patients(N)	Recurrences (mean±SD)
CsA-Ketotifen	16 §	0.81±1.11 §	15 §§	1.20±1.15 §§	15	-0.33±1.45
Ketotifen-CsA	15 §§	0.13±0.35 §§	18 §	0.83±1.04 §	15	-0.60±0.91
Total	31	0.48±0.89	33	1±1.09	30	-0.47±1.20*

*Wilcoxon Signed Rank Test $P=0.0371$; CsA=Cyclosporine A; SD= Standard deviation.

§ patients and recurrences during the first year of the study (no significant differences in the recurrence rate)

§§ patients and recurrences during the second year ($p<0.01$)

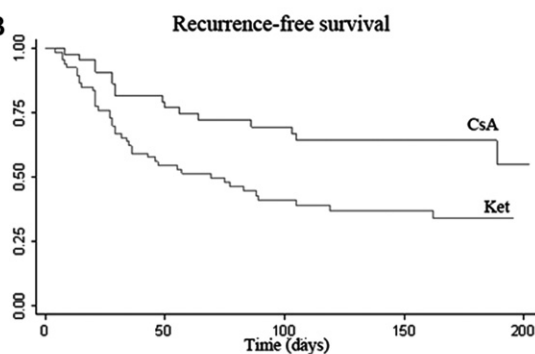
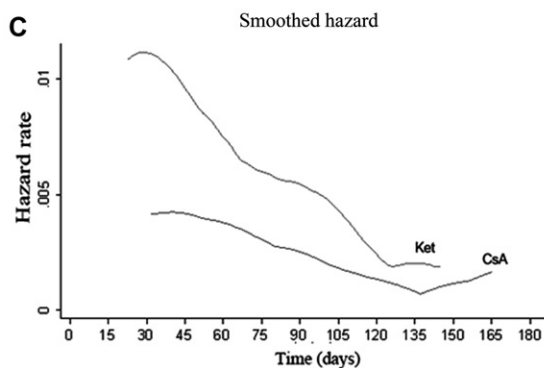
B**C**

FIG E2. The number of recurrences was significantly reduced when patients were treated with 0.05% cyclosporine with respect to 0.025% ketotifen (**A**). The cyclosporine group had significantly longer periods free of recurrences compared with the ketotifen group (**B**). Patients treated with ketotifen had a higher risk of recurrences after a flare-up episode than patients treated with cyclosporine (**C**). CsA, Cyclosporine; Ket, ketotifen.

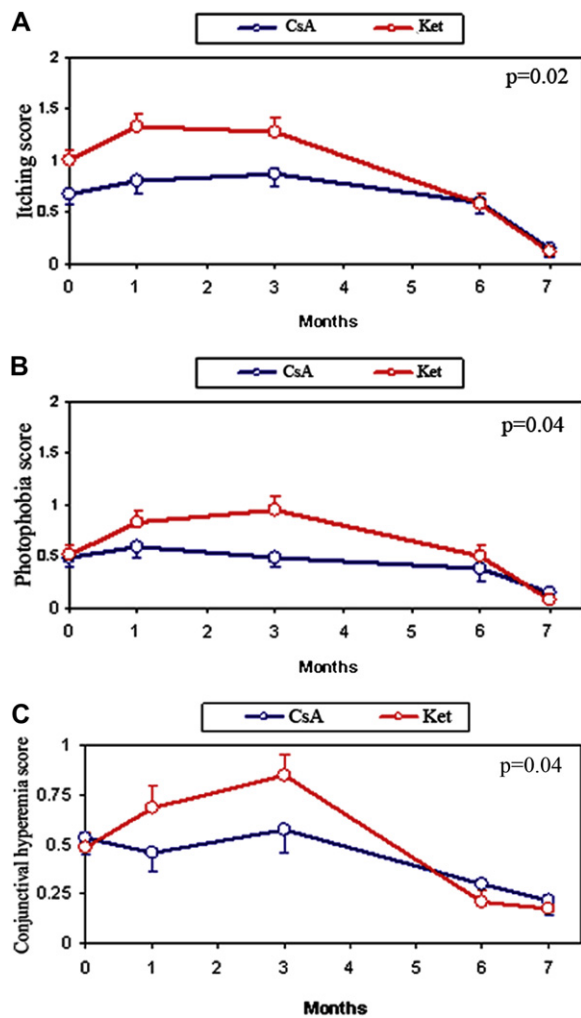


FIG E3. Itching, photophobia, and conjunctival hyperemia scores showed significant amelioration in patients treated with 0.05% cyclosporine eye drops compared with those seen in patients treated with 0.025% ketotifen eye drops. Data are expressed as means $\pm$ SEMs. CsA, Cyclosporine; Ket, ketotifen.

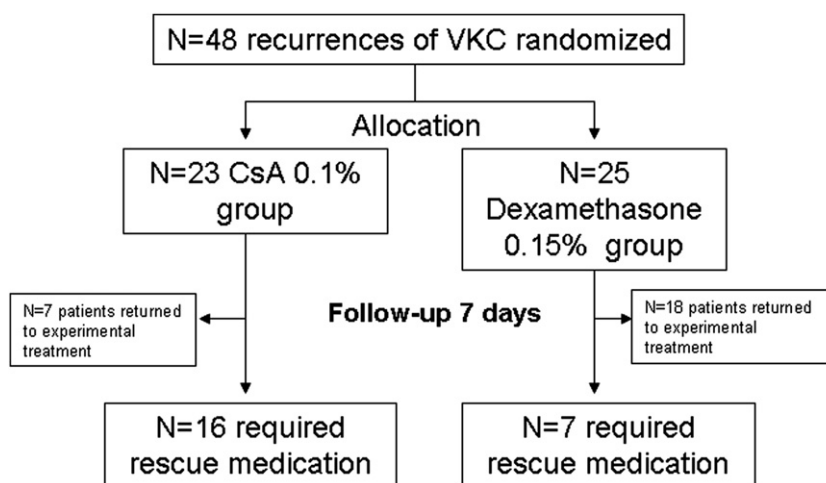


FIG E4. Forty-eight recurrences of ocular inflammation were randomized to receive either 0.1% cyclosporine eye drops or 0.15% dexamethasone eye drop 4 times daily for 7 days. A significantly higher number of recurrences treated with 0.1% cyclosporine eye drops ($n = 16$) required rescue medication after 7 days of treatment compared with recurrences treated with dexamethasone eye drops ($n = 7$).

TABLE E1. Patients' characteristics

Patients (n)	34
Sex	
Male	30 (88%)
Female	4 (12%)
Age (y)	
Range	6-33
Mean $\pm$ SD	14 $\pm$ 7
VKC type (n)	
Tarsal	20 (59%)
Limbal	9 (26%)
Mixed	5 (15%)
VKC course (n)	
Seasonal	22 (65%)
Perennial	12 (35%)
Patients with atopic associated diseases (n)	9 (26%)
Skin prick test responses (n)	
Positive	17 (50%)
Dpt	6
Olive tree pollen	2
Dpt and olive tree pollen	2
Cat dander	2
Graminae	2
Graminae and <i>Alternaria</i> species	2
<i>Alternaria</i> species	1
Negative	16 (47%)
Not done	1 (3%)

Dpt, Dematophagoides pteronyssinus.

TABLE E2. Topical 0.05% cyclosporine eye drops were significantly more effective in controlling itching, photophobia, and conjunctival hyperemia than 0.025% ketotifen fumarate eye drops

Variables (mean score $\pm$ SD)	Treatment	Baseline	After 1 mo	After 3 mo	After 6 mo	1 mo After discontinuation	P value
Itching	0.05% CsA	0.6 $\pm$ 0.8	0.8 $\pm$ 0.9	0.8 $\pm$ 0.9	0.5 $\pm$ 0.7	0.1 $\pm$ 0.6	.02
	0.025% Ket	1 $\pm$ 0.7	1.3 $\pm$ 0.7	1.3 $\pm$ 1.3	0.6 $\pm$ 0.7	0.1 $\pm$ 0.3	
Photophobia	0.05% CsA	0.4 $\pm$ 0.6	0.6 $\pm$ 0.7	0.5 $\pm$ 0.7	0.4 $\pm$ 0.9	0.2 $\pm$ 0.6	.04
	0.025% Ket	0.5 $\pm$ 0.6	0.7 $\pm$ 0.7	1 $\pm$ 1	0.6 $\pm$ 0.7	0.1 $\pm$ 0.3	
Secretion	0.05% CsA	0.4 $\pm$ 0.7	0.6 $\pm$ 0.9	0.9 $\pm$ 1	0.2 $\pm$ 0.6	0.1 $\pm$ 0.4	NS
	0.025% Ket	0.7 $\pm$ 0.3	0.8 $\pm$ 0.9	1.5 $\pm$ 0.9	0.6 $\pm$ 0.8	0.2 $\pm$ 0.7	
Tearing	0.05% CsA	0.2 $\pm$ 0.4	0.5 $\pm$ 0.8	0.5 $\pm$ 0.7	0.2 $\pm$ 0.5	0.1 $\pm$ 0.4	NS
	0.025% Ket	0.3 $\pm$ 0.1	0.6 $\pm$ 0.7	0.7 $\pm$ 0.7	0.3 $\pm$ 0.6	0.1 $\pm$ 0.2	
Redness	0.05% CsA	0.4 $\pm$ 0.7	0.6 $\pm$ 0.7	1 $\pm$ 1.1	0.3 $\pm$ 0.5	0.1 $\pm$ 0.5	NS
	0.025% Ket	0.6 $\pm$ 0.8	1 $\pm$ 0.9	1.1 $\pm$ 1	0.7 $\pm$ 0.5	0.1 $\pm$ 0.3	
Blurred vision	0.05% CsA	0.1 $\pm$ 0.3	0.2 $\pm$ 0.5	0.2 $\pm$ 0.5	0.1 $\pm$ 0.2	0.1 $\pm$ 0.2	NS
	0.025% Ket	0.1 $\pm$ 0.4	0.3 $\pm$ 0.6	0.5 $\pm$ 0.8	0 $\pm$ 0.2		
Total symptoms score	0.05% CsA	2.1 $\pm$ 2.7	3.3 $\pm$ 3.2	3.9 $\pm$ 3.6	1.7 $\pm$ 2.7	0.7 $\pm$ 2.5	NS
	0.025% Ket	3 $\pm$ 1.4	4.6 $\pm$ 3.2	6 $\pm$ 3.9	2.8 $\pm$ 2.6	0.6 $\pm$ 1.3	
Conjunctival hyperemia	0.05% CsA	0.5 $\pm$ 0.6	0.5 $\pm$ 0.7	0.5 $\pm$ 0.8	0.3 $\pm$ 0.5	0.2 $\pm$ 0.6	.04
	0.025% Ket	0.4 $\pm$ 0.5	0.6 $\pm$ 0.6	0.8 $\pm$ 0.8	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	
Mucous discharge	0.05% CsA	0.4 $\pm$ 0.7	0.4 $\pm$ 0.7	0.4 $\pm$ 0.7	0.2 $\pm$ 0.6	0.1 $\pm$ 0.3	NS
	0.025% Ket	0.4 $\pm$ 0.3	0.5 $\pm$ 0.3	0.8 $\pm$ 0.9	0.5 $\pm$ 0.9	0.3 $\pm$ 0.6	
Tarsal papillae	0.05% CsA	1.2 $\pm$ 0.9	1.2 $\pm$ 1	1.2 $\pm$ 0.8	1.2 $\pm$ 0.9	1.1 $\pm$ 0.9	NS
	0.025% Ket	1.1 $\pm$ 0.7	1.2 $\pm$ 0.8	1.2 $\pm$ 1	1.3 $\pm$ 0.9	1.2 $\pm$ 1	
Limbal papillae	0.05% CsA	0.4 $\pm$ 0.7	0.5 $\pm$ 0.8	0.6 $\pm$ 0.9	0.3 $\pm$ 0.6	0.1 $\pm$ 0.4	NS
	0.025% Ket	0.3 $\pm$ 0.4	0.5 $\pm$ 0.7	0.7 $\pm$ 1.1	0.4 $\pm$ 0.9	0.2 $\pm$ 0.8	
Trantas dot	0.05% CsA	0.1 $\pm$ 0.3	0.2 $\pm$ 0.5	0.2 $\pm$ 0.5	0.2 $\pm$ 0.5	0.1 $\pm$ 0.3	NS
	0.025% Ket	0.1 $\pm$ 0.3	0.3 $\pm$ 0.6	0.5 $\pm$ 0.9	0.2 $\pm$ 0.6	0.1 $\pm$ 0.1	
Superficial punctate keratitis	0.05% CsA	0.2 $\pm$ 0.7	0.3 $\pm$ 0.8	0.5 $\pm$ 0.9	0.3 $\pm$ 0.9	0.2 $\pm$ 0.5	NS
	0.025% Ket	0.2 $\pm$ 0.7	0.5 $\pm$ 0.4	0.6 $\pm$ 1.1	0.3 $\pm$ 0.5	0.2 $\pm$ 0.6	
Corneal ulcer	0.05% CsA	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0.2	0 $\pm$ 0.2	0 $\pm$ 0.2	NS
	0.025% Ket	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
Corneal neovascularization	0.05% CsA	0 $\pm$ 0	0 $\pm$ 0	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	0 $\pm$ 0.2	NS
	0.025% Ket	0.1 $\pm$ 0.4	0.1 $\pm$ 0.6	0.1 $\pm$ 0.2	0 $\pm$ 0.2	0 $\pm$ 0.2	
Total signs score	0.05% CsA	3 $\pm$ 2.9	3.5 $\pm$ 3.5	4 $\pm$ 4	3 $\pm$ 3.3	2.2 $\pm$ 2.7	NS
	0.025% Ket	3 $\pm$ 1.9	4.1 $\pm$ 2.4	5.1 $\pm$ 4	3 $\pm$ 1.9	2.2 $\pm$ 2.4	
Oxford score	0.05% CsA	0.3 $\pm$ 1	0.5 $\pm$ 1.2	0.7 $\pm$ 1.4	0.6 $\pm$ 1.4	0.3 $\pm$ 1	NS
	0.025% Ket	0.3 $\pm$ 1	0.8 $\pm$ 0.9	0.7 $\pm$ 1.2	0.5 $\pm$ 0.8	0.2 $\pm$ 0.8	

CsA, Cyclosporine; Ket, ketotifen; NS, not statistically significant.

TABLE E3. Topical ophthalmic 0.15% dexamethasone eye drops were significantly more effective in controlling the signs and symptoms of VKC than 0.1% cyclosporine eye drops

Variables (mean score $\pm$ SD)	Treatment	Baseline	After 1 wk	P value
Itching	0.1% CsA	2.1 $\pm$ 0.9	1.4 $\pm$ 0.9	<.0001
	0.15% Dex	2.3 $\pm$ 0.8	0.5 $\pm$ 0.9	
Photophobia	0.1% CsA	1.4 $\pm$ 1.1	1 $\pm$ 1	.0003
	0.15% Dex	1.5 $\pm$ 1	0.4 $\pm$ 0.7	
Secretion	0.1% CsA	1.8 $\pm$ 1.2	0.8 $\pm$ 1	.036
	0.15% Dex	1.8 $\pm$ 1	0.5 $\pm$ 0.9	
Tearing	0.1% CsA	1.2 $\pm$ 1	0.8 $\pm$ 1	.048
	0.15% Dex	1 $\pm$ 1	0.2 $\pm$ 0.5	
Redness	0.1% CsA	1.7 $\pm$ 1	1 $\pm$ 1.1	<.0001
	0.15% Dex	1.7 $\pm$ 1	0.3 $\pm$ 0.9	
Blurred vision	0.1% CsA	0.4 $\pm$ 0.7	0.4 $\pm$ 0.8	NS
	0.15% Dex	0.4 $\pm$ 0.8	0.1 $\pm$ 0.5	
Total symptoms score	0.1% CsA	8.7 $\pm$ 3.8	4.9 $\pm$ 4.3	<.0001
	0.15% Dex	8.7 $\pm$ 4	2 $\pm$ 4	
Conjunctival hyperemia	0.1% CsA	1.8 $\pm$ 0.9	0.9 $\pm$ 0.8	.0003
	0.15% Dex	1.6 $\pm$ 1	0.1 $\pm$ 0.5	
Mucous discharge	0.1% CsA	1.6 $\pm$ 0.9	0.8 $\pm$ 0.7	.015
	0.15% Dex	1.4 $\pm$ 0.9	0.4 $\pm$ 0.7	
Tarsal papillae	0.1% CsA	1.5 $\pm$ 0.9	1.5 $\pm$ 0.7	NS
	0.15% Dex	1.3 $\pm$ 0.9	1.4 $\pm$ 0.9	
Limbal papillae	0.1% CsA	0.8 $\pm$ 1	0.5 $\pm$ 0.9	NS
	0.15% Dex	0.6 $\pm$ 0.8	0.2 $\pm$ 0.5	
Trantas dot	0.1% CsA	1.4 $\pm$ 1	0.6 $\pm$ 0.8	NS
	0.15% Dex	1.2 $\pm$ 1	0.3 $\pm$ 0.6	
Superficial punctate keratitis	0.1% CsA	1.1 $\pm$ 1	0.7 $\pm$ 0.9	.0021
	0.15% Dex	1.2 $\pm$ 1.1	0.3 $\pm$ 0.7	
Corneal ulcer	0.1% CsA	0.02 $\pm$ 0.1	0.05 $\pm$ 0.2	NS
	0.15% Dex	0.05 $\pm$ 0.3	0.05 $\pm$ 0.3	
Corneal neovascularization	0.1% CsA	0.15 $\pm$ 0.6	0.02 $\pm$ 0.2	NS
	0.15% Dex	0 $\pm$ 0	0 $\pm$ 0	
Total signs score	0.1% CsA	8.6 $\pm$ 3.4	5.3 $\pm$ 3	.0013
	0.15% Dex	7.5 $\pm$ 3	3 $\pm$ 2.7	
Oxford score	0.1% CsA	1.8 $\pm$ 1.5	1.1 $\pm$ 1.4	.0008
	0.15% Dex	2.1 $\pm$ 1.7	0.4 $\pm$ 0.8	

CsA, Cyclosporine; Dex, dexamethasone; NS, not statistically significant.