• Clinical Research •

Efficacy and safety of cyclosporine 1% eye drops for the treatment of pediatric blepharokeratoconjunctivitis

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Received: 2025-06-05 Accepted: 2025-12-09

Abstract

● **AIM:** To evaluate the efficacy and safety of cyclosporine 1% (CsA) eye drops in patients affected by pediatric blepharokeratoconjunctivitis (PBKC).

● **METHODS:** This was a retrospective, single arm study of pediatric patients with PBKC. All patients received topical CsA 1% eye drops, administered three times daily for 2mo and then tapered during the third month. In the first treatment week, chloramphenicol and betamethasone eye drops were also given three times daily. Patients were examined at baseline (T0), 4wk (T1), 3mo (T2), and 12mo (T3). At each visit, slit-lamp evaluation of the anterior segment and anterior segment photography were performed. Disease activity and damage were assessed using the modified Hamada bimodal scoring system. Mean PBKC scores across time points were compared using one-way ANOVA, followed by Tukey's HSD post-hoc test.

● **RESULTS:** Thirty-six pediatric patients with PBKC were enrolled, six are excluded for incomplete follow-up, leaving 30 patients (11 males, 19 females; mean age 7.71±3.86y) for analysis. The baseline activity score was 1.60±0.62 and decreased significantly at all time points (T1: 0.53±0.51; T2: 0.34±0.76; T3: 0.47±0.86; P<0.001). Damage scores declined by 52% at T1, 53% at T2, and 70% at T3, with significant reductions at T2 and T3 versus baseline (P<0.01). No adverse events occur during the follow-up.

● **CONCLUSION:** CsA 1% eye drops effectively control the signs and symptoms of PBKC in pediatric patients and demonstrate a favorable safety profile, supporting their used as a valid therapeutic option in clinical practice.

● **KEYWORDS:** cyclosporine; pediatric blepharokeratoconjunctivitis; pediatrics

DOI:10.18240/ijo.2026.05.05

Citation: Masini M, Di Grande L, de Libero C, Marziali E, Danti G, Masi V, Simonetti G, Giovannini M, Mori F, Jeng BH, Caputo R. Efficacy and safety of cyclosporine 1% eye drops for the treatment of pediatric blepharokeratoconjunctivitis. *Int J Ophthalmol* 2026;19(5):878-882

INTRODUCTION

Pediatric blepharokeratoconjunctivitis (PBKC) is a frequently underdiagnosed, sight-threatening, chronic, and recurrent inflammatory eyelid margin disease associated with ocular surface involvement affecting children and adolescents. Its clinical spectrum includes chronic blepharitis, meibomitis, conjunctivitis, and corneal involvement ranging from superficial punctate keratitis to corneal infiltrates with vascularization and scarring[1-2]. The incidence of this pathology in the pediatric population is not known, but its spread is not insignificant: it is found in 12% to 15% of pediatric eye examinations[3-4]. The most frequent age of onset is between 3 and 5y, with rare cases of onset in individuals younger than 6mo and over 12y, and it is more frequent in the female population[5].

The pathogenesis of this condition primarily involves meibomian gland dysfunction (MGD), which are normally responsible for the secretion of proteins and lipids that contribute to the normal integrity and functionality of the tear film. Their dysfunction therefore causes the aforementioned clinical manifestations of the disease: recurrent chalazia, which is often the first warning sign of this pathology, and blepharitis, with frequent presence of crusting, along with conjunctival and eyelid hyperemia and edema. Unfortunately, the underlying mechanisms are not fully understood. The inflammatory and mechanical stimuli resulting from this dysfunction therefore

affect the conjunctiva and cornea, thus causing irritation and related signs and symptoms: hyperemia, keratitis, tearing, photophobia, and foreign body sensation[3]; in case of lack of or delayed adequate treatment, complications are frequent, such as the formation of corneal neovascularization, scars, and corneal ulcers, which result in reduced visual acuity and loss of vision[6-7].

The management of this condition is based on multiple interventions[8] that include daily cleaning of the eyelid margin with ophthalmic wipes and warm compresses, use of artificial tears, antibiotic therapy (the frequent discovery of *Staphylococcus aureus* in conjunctival/eyelid swabs in patients with PBKC justifies the use of topical or systemic antibiotics, which also have the benefit of exerting an anti-inflammatory action)[9-11], and local anti-inflammatory therapy with topical corticosteroids. While corticosteroids are extremely effective in reducing signs and symptoms of PBKC, they have important side effects in cases of prolonged use (*e.g.*, glaucoma, cataracts, infections). To minimize the need to resort to corticosteroid therapy, cyclosporine A (CsA)-based eye drops have long been used in the treatment of blepharoconjunctivitis and MGD, with concentrations ranging from 0.5% to 2.0%, in monotherapy or in combination with systemic antibiotics[12-17] with excellent results in terms of efficacy and safety.

In our center, the use of 1% CsA eye drops represents the standard of therapy for chronic PBKC as a steroid-sparing agent, for patients needing protracted therapy with steroids. In recent years we have been able to document excellent results concerning the clinical response and tolerability of this drug. However, the available literature on the use of topical CsA for treating PBKC is limited[15,18-19].

With this study, we aim to share the experience gained in recent years regarding the efficacy and safety of CsA 1% eye drops in our population of patients suffering from PBKC.

PARTICIPANTS AND METHODS

Ethical Approval We conducted a retrospective interventional, single arm, monocentric study based on standardized clinical charts and data on a cohort of pediatric patients with PBKC at the Meyer Children's Hospital IRCCS, Florence (Italy). The study was approved by the local Pediatric Ethics Committee at Meyer University Hospital, Florence, Italy (Approval No.579/CHILD/2024; protocol CICLO-BKC). All procedures were conducted in accordance with the Declaration of Helsinki and institutional guidelines. Protocol design and data review were done in collaboration with the Department of Ophthalmology and Scheie Eye Institute, University of Pennsylvania, Perelman School of Medicine, Philadelphia, USA. For all study participants, written informed consent was obtained. Between March 2015 and September 2022, we collected standardized clinical charts and data of consecutive patients affected by PBKC.

Inclusion criteria were: the clinical diagnosis of PBKC based on changes of the lid margin (telangiectasia, thickening, scarring), MGD, redness of the eye (conjunctival hyperemia), conjunctival chemosis, and inflammation of the cornea (punctate epithelial keratitis, corneal opacities, ulceration, thinning, vascularization, and scarring)[2], treatment with CsA 1% eye drops [galenic preparation compounded under aseptic conditions in our hospital laboratories, obtained by diluting 2 mL of a Sandimmun vial (CsA 50 mg/mL, Novartis) in 8 mL of Lacrimart (BAIF International Products New York S.n.c.)] three times daily for 2mo, then tapering to twice daily during the third month. After the third month, patients stopped treatment or were allowed to use CsA once daily or once every other day. Minimum follow-up of 12 mo.

Exclusion criteria were: patients younger than 2y or older than 18y, the presence of any systemic chronic infections, previous herpetic eye disease, malignancies or immunodeficiency, acne rosacea, known hypersensitivity to CsA, any systemic therapy for other atopic diseases, corticosteroid topical treatment in the previous 2wk, presence of inflammatory or degenerative pathologies of the ocular surface with the exception of PBKC, or inability to maintain satisfactory compliance with therapy administration.

During the first week, together with the CsA treatment, every patient received chloramphenicol and betamethasone eye drops three times a day. Patients' parents were trained to use eyelid wipes and warm compresses twice daily throughout the entire treatment period. The following data was collected for every enrolled patient at time 0 (T0: at the time of diagnosis, before the start of therapy), time 1 (T1: 4wk±2 since the beginning of therapy), time 2 (T2: 3±1mo), and time 3 (T3: 12±3mo): slit lamp bio-microscopy of the anterior segment with grading evaluation of PBKC: conjunctival hyperemia, presence of new vessels, corneal leukomas, conjunctival edema, eyelid sprain; and photographs of the anterior segment.

Every examination was graded according to the modified Hamada validated bimodal activity and damage score[6] (Table 1). Disease activity scores ranged from A0 (no active inflammation) to A3 (severe inflammation), and those clinical manifestations are reversible with adequate treatment. Damage score was graded from D0 (no damage) to D3 (severe). Patients were examined by the same trained ophthalmologist (de Libero C). Demographic and clinical data were also collected for each study participant.

All data were analyzed using IBM SPSS version 26 statistical software (IBM, Armonk, New York, USA). One-way analysis of variance (ANOVA) and Tukey's honest significance difference (HSD) test were used to compare mean scores between different times of exposure. *P*-values less than 0.05 were considered statistically significant.

Table 1 Modified bimodal activity and damage score (adapted from Hamada *et al*[6], 2012)

Score	Grade	Activity (A)	Damage (D)
0	None	Absence of conjunctival inflammation, ocular surface ulceration	Absence of lid margin distortion, conjunctival scars, corneal vascularization, thinning
1	Mild	Any of conjunctival inflammation and/or edema, peripheral new vessel <3h	Any of mild lid distortion, mild conjunctival fibrosis, fibrovascular pannus <3h
2	Moderate	Any of extensive or marked conjunctival hyperemia, conjunctival stromal oedema, active peripheral new vessels >3h and/or extending to the pupil margin	Any of moderate lid distortion, moderate subconjunctival fibrosis (<50% shortening of either fornix), fibrovascular pannus involving >3h and/or extending to the pupil margin, peripheral corneal thinning (<33% loss of tissue)
3	Severe	Any of inflammation in all quadrants, severe conjunctival oedema, conjunctival or corneal ulceration, corneal perforation, active new vessels extending to central zone	Any of severe lid distortion, severe subconjunctival fibrosis (>50% shortening of either fornix), fibrovascular pannus extending to the central zone, central corneal scarring, central corneal thinning, significant peripheral corneal thinning (>33% loss of tissue)

RESULTS

Thirty-six consecutive patients (age 2-15y) who satisfied the inclusion criteria were included in the study. Six patients were excluded because they did not comply with the visits schedule. The results of each patient were analyzed at T1, T2, and T3 at the end of follow-up. Eleven males and nineteen females (mean age 7.71±3.86y) completed the follow-up period.

The patients' demographic data at baseline are summarized in Table 2. The distribution of each single value is shown in Figure 1 at baseline and during the follow-up period.

Average values for activity (A) and damage (D) scores are shown respectively in Tables 3 and 4 at T0, T1, T2, and T3. Activity scores showed a marked reduction when comparing pre-treatment values [mean value: 1.6, standard deviation (SD) 0.62] with both post-treatment scores T1, T2 and T3 (0.53±0.51 and 0.34±0.76, respectively), with statistically significant differences between T0 and every other subsequent timepoint. We recorded a 67% drop in the activity score between T0 and T1 and a 75% reduction in the score between T0 and T2. There was a 71% drop in the mean A value between T0 and T3.

We found a decreasing trend when analyzing the damage scores, with each subsequent observation showing progressively lower scores (Figure 2), decreasing by 52%, 53% and 70% when comparing T0 with T1, T2, and T3, respectively. Differences in mean values were not statistically significant between T0 and T1, but statistically significant reduction was recorded when comparing either T2 and T3 with both T0 and T1 (P<0.01; Table 4). Differences between T2 and T3 were also not statistically significant.

No patients required additional steroid or antibiotic therapy during the treatment period. No side effects or adverse events were recorded during the entire follow up regarding the safety profile of CsA treatment.

DISCUSSION

PBKC is a sight-threatening, chronic, and recurrent inflammatory eyelid margin disease associated with ocular surface involvement affecting children and adolescents[2,20]. The diagnosis of PBKC is clinical and mainly based on the changes of the lid margin, MGD, redness of the eye, conjunctival chemosis and inflammation of the corneal surface[2].

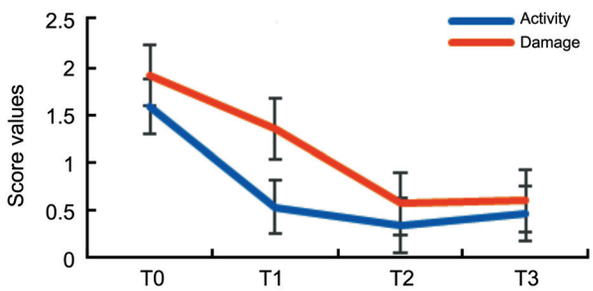

Figure 1 Evolution of mean activity and damage score during follow-up T0: Time at diagnosis; T1: Time after 4wk since the beginning of therapy; T2: Time after 3mo since the beginning of therapy; T3: Time after 12mo.

Table 2 Baseline demographic data of the study patients

Demographic data	Values
Subjects (*n*)	30
Female:male	1.91
Age (mean±SD, y)	7.71±3.86

SD: Standard deviation.

Different medications have been routinely proposed to treat PBKC in children. Topical and systemic antibiotics are used in PBKC patients mainly for their double antibiotic and anti-inflammatory action: *S.aureus* and *S.epidermidis* are frequently present on conjunctival and eyelid swabs in PBKC patients[11]. The most used systemic treatment in PBKC patients is erythromycin[9]. However, more recently, other macrolide antibiotics such as azithromycin have also been used both for their antibacterial and anti-inflammatory properties. Different topical steroids such as dexamethasone, prednisolone and fluorometholone[2,6,9,21-23], have also been used for chronic PBKC, but with the risk of severe adverse events with long term use.

To date, a consensus on the most effective treatment modality for the use of CsA in PBKC has not been reached. In 2007, Doan *et al*[24] reported the efficacy of topical CsA 2% as a rescue medication when topical azithromycin and lid hygiene failed in 19 PBKC patients. A different concentration of the medication (CsA 0.5%) was described by Ismail *et al*[19] in 2012 to treat a case of a BKC complicated by severe corneal neovascularization. The authors reported the complete regression of the corneal neovascularization few days after the CsA 0.5% administration. Furthermore, topical CsA 1%

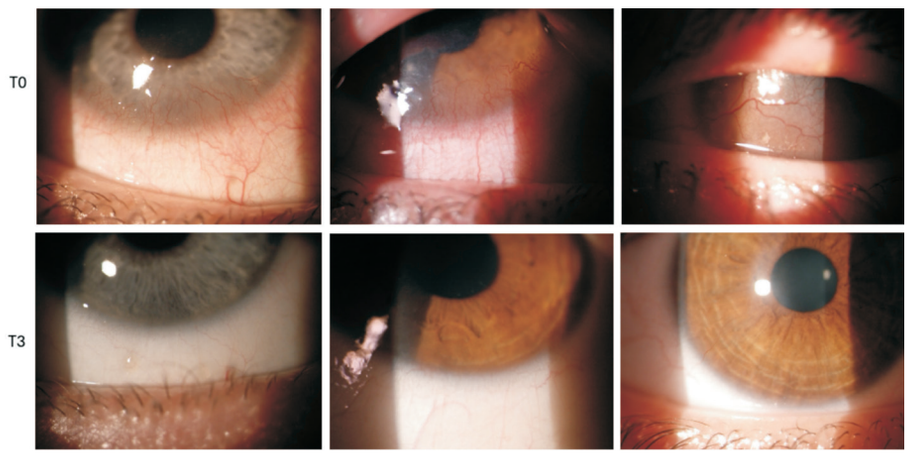

Figure 2 Evolution of fibrovascular pannus at baseline (T0) and after treatment (T3).

Table 3 Average activity (A) scores of the study patients at follow-up visits

Groups	Count	Sum	Mean	SD	Difference *vs* T0 (%)
A-T0	30	48	1.60	0.62	
A-T1	30	16	0.53	0.51	-67%
A-T2	30	10	0.34	0.76	-75%
A-T3	30	14	0.47	0.86	-71%
Activity score comparison					
Evaluation pairs			Tukey *P* values		
T0 *vs* T1			<0.01		
T0 *vs* T2			<0.01		
T0 *vs* T3			<0.01		
T1 *vs* T2			0.66		
T1 *vs* T3			0.89		
T2 *vs* T3			0.87		

SD: Standard deviation; T0: At the time of diagnosis, before the start of therapy; T1: 4wk±2 since the beginning of therapy; T2: 3±1mo; T3: 12±3mo.

Table 4 Average damage (D) scores of the study patients at follow-up visits

Groups	Count	Sum	Mean	SD	Difference *vs* T0 (%)
D-T0	30	58	1.93	0.78	
D-T1	30	41	1.37	0.93	-52%
D-T2	30	17	0.57	0.90	-53%
D-T3	30	18	0.60	0.93	-70%
Damage score comparison					
Evaluation pairs			Tukey *P* values		
T0 *vs* T1			0.07		
T0 *vs* T2			<0.01		
T0 *vs* T3			<0.01		
T1 *vs* T2			<0.01		
T1 *vs* T3			<0.01		
T2 *vs* T3			0.90		

SD: Standard deviation; T0: At the time of diagnosis, before the start of therapy; T1: 4wk±2 since the beginning of therapy; T2: 3±1mo; T3: 12±3mo.

combined with oral azithromycin was described by Choi and Djalilian[25] with good results in terms of tolerability and corneal transparency.

Recently, Dahlmann-Noor *et al*[15] published a large retrospective study on 145 children and young adults of different ethnicities affected by PBKC. They used CsA 1% once or a maximum of twice daily, although a small group had to increase the dosage per day or add topical steroids. They did not report any severe adverse effects, and they reported that twice daily administration of CsA 1% significantly reduced the use of topical steroids and hospital visits, and they found that children tolerated CsA better than adults, as stinging was a far less common reason for discontinuation than in dye eye disease (DED) reports.

In this study, we treated chronic PBKC patients with CsA 1% as a steroid-sparing agent. More specifically, we described the safety and efficacy of CsA 1% eye drops three times daily in a cohort of pediatric Caucasian patients with chronic PBKC. To date, there is no commercially available ophthalmic preparation of CsA 1% in Italy, even though this medication is widely used in the treatment of vernal keratoconjunctivitis (VKC)[26-27], and even in adenovirus keratitis[28].

To the best of our knowledge, our study is the first to report a standardized protocol for treating patients affected by PBKC. Although it is not a prospective study, it was conducted using a standardized clinical chart and data, reducing the bias among different patients. Our results show the good efficacy of topical CsA in reducing the inflammation in PBKC. As was logical to expect, CsA is much more effective in active lesions (Activity score) than in those already in the scarring stage (Damage score).

Regarding the safety profile of this treatment, during the follow-up, no patients presented with recurrences or adverse events, and none of them required steroid administration. Although our findings show excellent tolerability, individual patient experiences may vary, and clinicians should be aware of the potential side effects for discomfort in certain cases. Considering the risk/benefit ratio of the treatment, CsA 1% could be safely used, and could replace steroids and antibiotics in the treatment of the disease. Further prospective studies, with a longer follow-up are needed to better corroborate our speculative hypothesis.

The main limitations of this study are its retrospective nature, the relatively short follow-up period, and the absence of a control group. Therefore, it was not possible to directly compare the treatment and the natural history of the disease. To ascertain the true efficacy of topical CsA in the management of PBKC, a double-masked, randomized, vehicle-controlled trial—representing the gold standard of evidence—is essential. Moreover, extensive multinational data will be needed to confirm our findings in different populations.

In conclusion, our study showed that topical 1% CsA eye drops are an effective and safe treatment for PBKC. We provide evidence confirming the efficacy of CsA 1% eye drops in controlling the signs and symptoms of PBKC, with an excellent safety profile.

ACKNOWLEDGEMENTS

Conflicts of Interest: Masini M, None; **Di Grande L,** None; **de Libero C,** None; **Marziali E,** None; **Danti G,** None; **Masi V,** None; **Simonetti G,** None; **Giovannini M** reports personal fees from Sanofi, Thermo Fisher Scientific; **Mori F,** None; **Jeng BH,** None; **Caputo R,** None.

REFERENCES

1 Rousta ST. Pediatric blepharokeratoconjunctivitis: is there a 'right' treatment. *Curr Opin Ophthalmol* 2017;28(5):449-453.

2 Morales-Mancillas NR, Velazquez-Valenzuela F, Kinoshita S, *et al*. Definition and diagnostic criteria for pediatric blepharokeratoconjunctivitis. *JAMA Ophthalmol* 2024;142(1):39-47.

3 Hammersmith KM. Blepharokeratoconjunctivitis in children. *Curr Opin Ophthalmol* 2015;26(4):301-305.

4 Jie Y, Wen Y. Focus on the diagnosis and treatment of blepharokeratoconjunctivitis in children. *Zhonghua Yan Ke Za Zhi* 2022;58(8):561-564.

5 Farpour B, McClellan KA. Diagnosis and management of chronic blepharokeratoconjunctivitis in children. *J Pediatr Ophthalmol Strabismus* 2001;38(4):207-212.

6 Hamada S, Khan I, Denniston AK, *et al*. Childhood blepharokeratoconjunctivitis: characterising a severe phenotype in white adolescents. *Br J Ophthalmol* 2012;96(7):949-955.

7 Rodríguez-García A, González-Godínez S, López-Rubio S. Blepharokeratoconjunctivitis in childhood: corneal involvement and visual outcome. *Eye (Lond)* 2016;30(3):438-446.

8 O'Gallagher M, Bunce C, Hingorani M, *et al*. Topical treatments for blepharokeratoconjunctivitis in children. *Cochrane Database Syst Rev* 2017;2(2):CD011965.

9 Jones SM, Weinstein JM, Cumberland P, *et al*. Visual outcome and corneal changes in children with chronic blepharokeratoconjunctivitis. *Ophthalmology* 2007;114(12):2271-2280.

10 Meisler DM, Raizman MB, Traboulsi EI. Oral erythromycin treatment for childhood blepharokeratitis. *J Am Assoc Pediatr Ophthalmol Strabismus* 2000;4(6):379-380.

11 Wong IBY, Nischal KK. Managing a child with an external ocular disease. *J Am Assoc Pediatr Ophthalmol Strabismus* 2010;14(1):68-77.

12 Prabhasawat P, Tesavibul N, Mahawong W. A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibomian gland dysfunction. *Cornea* 2012;31(12):1386-1393.

13 Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Adv Ther* 2009;26(6):651-659.

14 Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin a ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease. *Ophthalmology* 2000;107(5):967-974.

15 Dahlmann-Noor AH, Roberts C, Muthusamy K, *et al*. Cyclosporine A 1mg/ml in pediatric blepharokeratoconjunctivitis: case series of 145 children and young people. *Ocul Surf* 2022;25:37-39.

16 Sabeti S, Kheirkhah A, Yin J, *et al*. Management of meibomian gland dysfunction: a review. *Surv Ophthalmol* 2020;65(2):205-217.

17 Chidi-Egboka NC, Fan L, Qureshi M, *et al*. Evidence on the use of topical ciclosporin for ocular surface disease: a systematic review and meta-analysis. *Clin Exp Ophthalmol* 2025;53(5):470-492.

18 Auw-Hädrich C, Reinhard T. Treatment of chronic blepharokeratoconjunctivitis with local calcineurin inhibitors. *Ophthalmologe* 2009;106(7):635-638.

19 Ismail AS, Taharin R, Embong Z. Topical cyclosporin as an alternative treatment for vision threatening blepharokeratoconjunctivitis: a case report. *Int Med Case Rep J* 2012;5:33-37.

20 Ortiz-Morales G, Ruiz-Lozano RE, Morales-Mancillas NR, *et al*. Pediatric blepharokeratoconjunctivitis: a challenging ocular surface disease. *Surv Ophthalmol* 2025;70(3):516-535.

21 Hosseini K, Lindstrom R, Hutcheson J. A Phase III clinical study to evaluate the efficacy of combined azithromycin and dexamethasone in the treatment of blepharoconjunctivitis. *Clin Ophthalmol* 2013;7:2225-2234.

22 Torkildsen GL, Cockrum P, Meier E, *et al*. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. *Curr Med Res Opin* 2011;27(1):171-178.

23 Viswalingam M. Blepharokeratoconjunctivitis in children: diagnosis and treatment. *Br J Ophthalmol* 2005;89(4):400-403.

24 Doan S, Gabison E, Chiambaretta F, *et al*. Efficacy of azithromycin 1.5% eye drops in childhood ocular rosacea with phlyctenular blepharokeratoconjunctivitis. *J Ophthalmic Inflamm Infect* 2013;3(1):38.

25 Choi DS, Djalilian A. Oral azithromycin combined with topical anti-inflammatory agents in the treatment of blepharokeratoconjunctivitis in children. *J Am Assoc Pediatr Ophthalmol Strabismus* 2013;17(1):112-113.

26 Pucci N, Novembre E, Cianferoni A, *et al*. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002;89(3):298-303.

27 Caputo R, Di Grande L, de Libero C, *et al*. Efficacy of a cationic emulsion of cyclosporine in moderate vernal keratoconjunctivitis. *Cornea* 2024;43(2):228-232.

28 Jeng BH, Holsclaw DS. Cyclosporine a 1% eye drops for the treatment of subepithelial infiltrates after adenoviral keratoconjunctivitis. *Cornea* 2011;30(9):958-961.