



Application of topical 2% cyclosporine A in inflammatory ocular surface diseases

Leyla Asena · Dilek Dursun Altınörs

Received: 8 September 2022 / Accepted: 22 June 2023 / Published online: 7 July 2023
© The Author(s), under exclusive licence to Springer Nature B.V. 2023

Abstract

Purpose To report our experience with the 2% cyclosporin A (CsA) in a series of challenging inflammatory ocular surface diseases due to different etiologies.

Methods The records of patients who received topical 2% CsA for different indications were reviewed retrospectively. Demographic characteristics, indications for treatment, patient symptoms and clinical findings were recorded.

Results Fifty-two eyes of 52 patients were included. Mean age was 43.2 ± 14.3 (11–66) years with a F/M ratio of 34/18. Indications included pediatric acne rosacea ($n=4$), adenoviral corneal subepithelial infiltrates ($n=12$), filamentary keratitis ($n=14$), pterygium recurrence ($n=15$), herpetic marginal keratitis ($n=2$) and graft versus host disease ($n=5$ patients). Mean duration of treatment was 7.3 ± 2.8 (3–10) months. Forty-three (83%) patients reported favorable outcome with improvement in symptoms after a mean time of 4.4 ± 2.7 (2–6) months.

Conclusions Topical 2% CsA may address the needs of different cases with ocular surface inflammation, as a safe option for long-term therapy.

Keywords Inflammation · Cornea · Ocular surface · Safety · Topical cyclosporin A

Introduction

Ocular surface diseases comprise a large spectrum of eye disorders with variable severity and different etiologies. In most of the chronic ocular surface disorders, the common mechanism leading to ocular surface damage is ongoing inflammation [1]. Therefore, the mainstay of treatment is anti-inflammatory medication and most commonly topical corticosteroids. However, topical corticosteroids are only suitable for short term treatment because of their well-known side effects such as cataract formation and glaucoma. Chronic ocular surface inflammation necessitates the use of long-term anti-inflammatory medication and therefore, immunomodulatory agents have become important tools for the management of these disorders [2].

Cyclosporine A (CsA) has been used successfully as a systemic immunomodulator for the past few decades. CsA modulates the immune response pathway by suppressing activation of T lymphocytes. It acts as a calcineurin inhibitor and suppresses transcription of the IL-2 gene and other T cell activation genes. It has also been shown to inhibit apoptosis or programmed cell death of ocular surface epithelial cells [1, 2]. Thus, it can target the two main pathogenic

L. Asena (✉) · D. Dursun Altınörs
Faculty of Medicine, Department of Ophthalmology,
Baskent University, Fevzi Çakmak Caddesi, Bahçelievler,
06490 Ankara, Turkey
e-mail: leylaerk@yahoo.com

mechanisms responsible for ocular surface damage due to inflammatory diseases.

Topical cyclosporine A 0.05% emulsion was approved by the FDA in 2003 for the treatment of dry eye disease. A cationic emulsion formulation containing 0.1% (1 mg/mL) cyclosporine A (Ikervis, Santen, Japan) was later introduced into the market, to address the need for higher concentrations. These emulsions have also been investigated for treatment of other ocular surface disorders that may have an immune-based inflammatory component. Topical 0.05 and 0.1% CsA were found to be effective for the management of contact lens intolerance, graft versus host disease, posterior blepharitis, post-LASIK dry eye, atopic keratoconjunctivitis and herpetic stromal keratitis in various studies [2–6]. Although these relatively low concentrations were found to be effective in alleviating inflammatory signs and symptoms in most studies [7–9], higher concentrations of cyclosporine A up to 2% were used for different indications with promising results and a high safety profile [10–15]. Among these are childhood phlyctenular keratoconjunctivitis [10], herpes simplex virus immune stromal keratitis [11], Thygeson superficial punctate keratitis [12], atopic [13] and vernal [14] keratoconjunctivitis. Although, the minimal concentration of cyclosporine in an oil-based pharmacy formulation for controlling shield ulcers associated with vernal keratoconjunctivitis was reported to be 1% [15], to our knowledge there are no studies demonstrating the superiority of higher concentrations of CsA for different indications. In this article, we aim to report our experience with 2% CsA formulation in a series of challenging inflammatory ocular surface diseases due to different etiologies which were unresponsive to treatment with the commercial 0.1% CsA.

Materials and methods

The study was approved by the Institutional Review Board of Baskent University Faculty of Medicine and adhered to the tenets of the Declaration of Helsinki. The records of patients who received topical 2% CsA for different off-label indications between March 2018 and March 2019 were reviewed retrospectively. Topical 2% CsA was prepared in the hospital pharmacy by dilution of the intravenous preparation 50 mg/mL cyclosporine in macrogolglycérol

ricinoleate. This concentration is routinely used in our clinic for different recalcitrant ocular surface inflammatory diseases, since it is the highest concentration reported to be used in the literature, with promising results and no serious adverse effects [10–15]. Patients receiving CsA for the treatment of uncomplicated dry eye were excluded since the purpose of the current study was to evaluate efficiency for variable off-label indications with ocular surface inflammation. Patients with suspected non-compliance to treatment and follow-up for less than 3 months were also excluded.

Treatment with topical 2% CsA was considered if the patients experienced flare ups or non-resolving active inflammation requiring ongoing treatment of topical steroids and were unresponsive to commercially available 0.1% CsA used up to 4 times a day for 12 weeks. Duration and dosage of topical administration of 2% CsA were decided by an experienced ophthalmologist (DDA) on a patient basis depending on the severity of signs and symptoms at presentation and follow-up, as well as the nature of the presenting ocular surface disease.

Demographic characteristics (age and gender), indications for treatment, patient symptoms and clinical findings at the initial and last follow-up visits, treatment regimen before the initiation of CsA, duration of treatment with CsA, administered dosage, pre- and posttreatment best corrected visual acuity and complications during treatment were recorded. In bilateral cases, the eye with most prominent involvement was selected for statistical analysis.

Outcome of treatment was determined as favorable when patient symptoms and clinical manifestations improved during treatment. Clinical outcome was defined based on clinical parameters on follow-up as described previously [16]: (1) resolved: when the signs and symptoms subsided completely for at least 1 month with no requirement of further 2% CsA treatment; (2) stable: when the disease did not resolve nor worsened with ongoing 2% CsA and the ocular surface was free from visibly detectable inflammation; (3) active: flare up of condition or active inflammation requiring additional treatment such as topical steroids and (4) intolerant: when patient on 2% CsA experienced burning sensation and discomfort necessitating discontinuation of the drug. The treatment was considered as ‘favorable’ if outcome 1 (resolved) or outcome 2 (stabilized) was achieved. In patients

with favorable outcome, time until the resolution of symptoms was recorded.

Treatment with 2% CsA qid was stopped when ‘favorable’ outcome was achieved, or the inflammation was still active after 8 weeks requiring additional treatment such as topical steroids. In patients with favorable outcome, maintenance therapy with 2% CsA was continued two times a day for 3–9 months. There was no intolerance necessitating discontinuation of the drug in the current study.

Data were tabulated and analyzed with the IBM® SPSS® Statistics 19.0 (SPSS Inc., Chicago IL, USA) software. McNemar’s test was used to determine if there were any differences between visual acuities, clinical signs and symptoms before and after the treatment period. A *p* value less than 0.05 was considered as statistically significant. Case descriptions were included for representative cases for different indications.

Results

A total of 52 eyes of 52 patients were included in the study. Mean age of the patients was 43.2 ± 14.3 (11–66) years with a F/M ratio of 34/18. Indications for the topical use of 2% CsA included pediatric acne rosacea (4 patients), adenoviral corneal sub-epithelial infiltrates (12 patients), filamentary keratitis (14 patients), early onset pterygium recurrence (15 patients), herpetic marginal keratitis (2 patients) and graft versus host disease (5 patients). Before the initiation of 2% CsA, all patients were receiving topical non-preserved artificial tears and topical

0.1% CsA 4×1. Forty-seven patients were on topical corticosteroids with variable potency and dosage, 2 patients with marginal herpetic keratitis were on topical and systemic antiviral medication and 4 patients with pediatric acne rosacea were receiving topical and systemic antibiotics. Duration of follow-up before the initiation of 2% CsA was 15.4 ± 3.1 (12–19) weeks. Topical CsA concentration was increased to 2% in all cases due to limited or unfavorable response to the ongoing treatment. Topical corticosteroid treatment was tapered and stopped in 7–10 days after initiation of topical 2% CsA. Mean duration of treatment with topical 2% CsA (qid and bid) was 7.3 ± 2.8 (3–10) months. The daily dosage of 2% CsA was 4×1 for at least 3 weeks in patients with favorable outcome, then maintenance therapy with 2% CsA bid was used. In patients with active inflammation despite the use of 2% CsA qid for 8 weeks, additional treatment options were implemented, according to disease etiology. Reported symptoms, clinical signs and visual acuity at the first and last visits are shown in Table 1. Frequency in signs and symptoms decreased significantly at the end of the follow-up. Visual acuity was stable in 40 (77%) patients and increased in 12 (23%) patients.

Ocular stinging and mild hyperemia upon instillation of topical CsA were observed in 12 patients (23%). Cessation of treatment was not necessary in any of these cases. No other local or systemic side effects were observed. Serum BUN and creatinine levels were measured every 3 months in patients receiving topical 2% CsA. All results were within normal limits. Forty-three (83%) out of 52 patients reported favorable outcome with improvement of symptoms in a mean time of 4.4 ± 2.7 (2–6) months.

Table 1 Reported symptoms, clinical signs and visual acuity at the first and last visits

	Number of eyes at presentation (%)	Number of eyes at the last visit (%)	<i>p</i> ^a value
Blurred vision	32 (62%)	14 (27%)	0.03*
Redness/conjunctival hyperemia	29 (56%)	10 (19%)	0.02*
Stinging/ocular discomfort	28 (54%)	9 (17%)	0.01*
Photophobia	34 (65%)	16 (31%)	0.03*
VA \geq 20/40	36 (69%)	46 (88%)	0.45
VA 20/50–20/100	13 (25%)	6 (12%)	0.21
VA \leq 20/125	3 (6%)	0 (0%)	0.65

^aMcNemar’s test and

*Statistically significant

Case descriptions

Below, case descriptions are included for representative cases with pediatric acne rosacea, filamentary keratitis, adenoviral corneal subepithelial infiltrates and early onset pterygium recurrence. These cases were chosen for further description since clinical results with topical 2% CsA treatment were not reported extensively in previous literature for these diseases.

Case 1

A 14-year-old girl was referred to our clinic with complaints of foreign body sensation, burning, photophobia, redness and recurrent hordeolum formation. She had used different topical medications including antibiotics, corticosteroids and CsA 0.05 and 0.1% in the past 3 years, without significant improvement in her signs and symptoms. She also had recurrent papules and pustules on her hands and feet. Visual acuity was 20/20 in the right eye and 20/25 in the left eye. There was bilateral conjunctival hyperemia and ciliary injection. Peripheral corneal subepithelial immune infiltrates were observed

in her right eye. There was corneal vascularization in the nasal quadrant and a vascularized pannus was observed on the nasal paracentral cornea. (Fig. 1).

Treatment was started with topical preservative-free artificial tears (Refresh; Allergan, Irvine, CA) 4×1, topical unpreserved dexamethasone (Dexasine SE; Liba Laboratories, İstanbul, Turkey) 3×1 which was tapered and used for a total of 10 days, topical 2% CsA 4×1 and systemic tetracycline 100 mg (Monodoks; Deva Pharmaceuticals, Kocaeli, Turkey) 1×1. Lid hygiene and warm compresses were advised as well. Dermatology consultation was performed. She was diagnosed as pediatric acne rosacea. At the control visit, 3 weeks later, her complaints had decreased. Vascularization and pannus on the left eye had decreased. The immune infiltrates in the right eye were fading and less prominent (Fig. 2).

Maintenance treatment was advised as topical 2% CsA 2×1 and preservative-free artificial tears 4×1. Corneal vascularization has been stable with minor symptoms during a follow-up of 9 months. Her visual acuity was 20/20 in both eyes at the last visit. Serum BUN and creatinine levels were measured every 3 months and were within normal limits.

Fig. 1 Anterior segment photographs of the patient showing bilateral conjunctival hyperemia and ciliary injection **a, b, c** and **d**, peripheral corneal subepithelial immune infiltrates in the right eye (**a** and **c**) and corneal vascularization in the nasal quadrant with a vascularized pannus on the nasal paracentral cornea of the left eye (**b** and **d**). The patient was on topical 0.1% cyclosporine A and unpreserved artificial tears, both qid, for the last 3 months

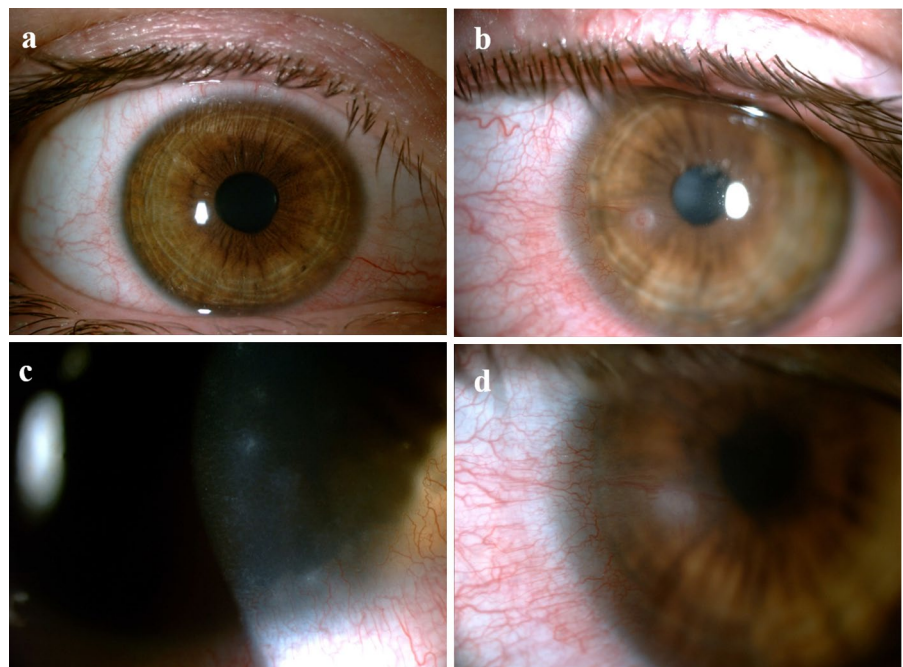
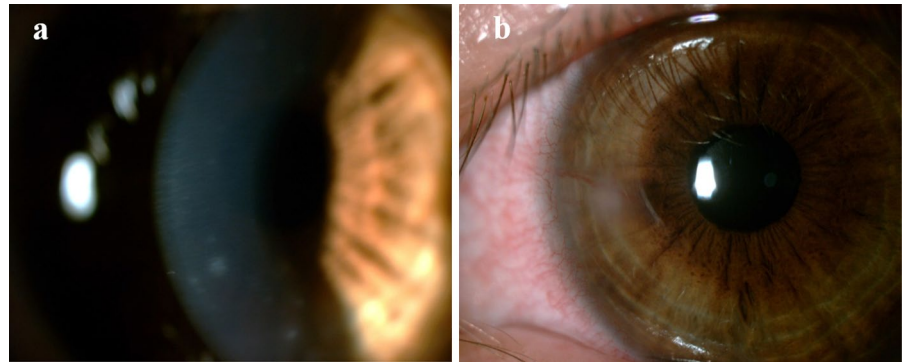


Fig. 2 Anterior segment images of the patient taken 4 weeks after the onset of treatment with topical 2% cyclosporine A. The immune infiltrates in the right eye faded and were less prominent (a). Vascularization and pannus on the left eye had decreased (b)



Case 2

A 48-year-old woman with known Sjogren's Syndrome admitted to our clinic with burning, foreign body sensation, photophobia, and decreased vision in both eyes. She was using systemic hydroxychloroquine 200 mg daily. She did not have any other known systemic or ocular diseases. Visual acuity was 20/25 in both eyes. Biomicroscopic examination revealed punctate epithelial erosions in the interpalpebral central cornea with few corneal filaments, in both eyes. Tear break up time was 4 s and Schirmer I test result was 2/2 mm in both eyes. Treatment was started with topical preservative-free artificial tears 4×1, topical 0.1% cyclosporine A 4×1 and carbomer containing ophthalmic gel 1×1 at bedtime. At the 12th week visit, there was no improvement in her symptoms. Biomicroscopic examination revealed increased corneal filaments. Topical N-acetylcysteine 4×1 was

added to the ongoing treatment and punctum occlusion was performed, but there was only limited improvement at the 10th day follow-up visit. Topical cyclosporine A concentration was increased to 2%, applied 4×1. After 3 weeks, the filaments were not observed and there was no corneal staining (Fig. 3). Visual acuity was 20/20 in both eyes. No recurrence was observed during a follow-up period of 5 months under maintenance treatment with 2% CsA bid.

Case 3

A 43-year-old female patient had undergone sutureless pterygium excision with conjunctival autograft implantation using fibrin glue, from her left eye, 3 months ago. She was on prednisolone acetate containing drops 1×1 when she was admitted to the clinic with increased redness in her eye. It was observed that the graft was dislocated temporally,

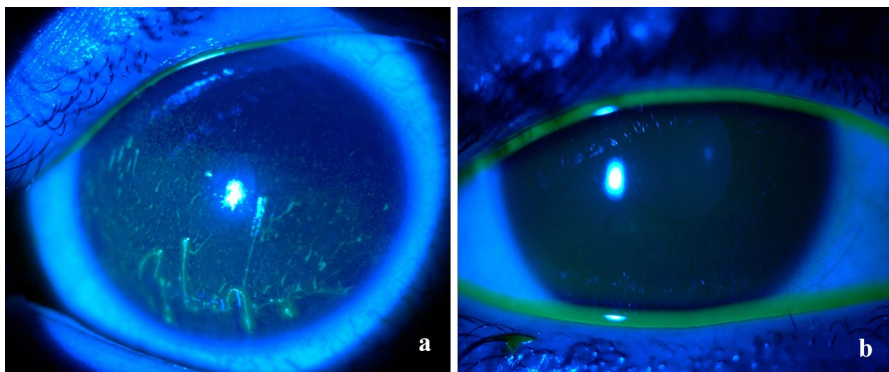


Fig. 3 Anterior segment photograph of the right eye showing punctate epithelial keratitis and corneal filaments under treatment with topical preservative-free artificial tears 4×1, topical 0.1% cyclosporine A 4×1 and carbomer containing ophthalmic gel 1×1 at bedtime (a). Anterior segment photograph at the 3rd week of treatment topical 2% cyclosporine A shows a healed ocular surface without any corneal filaments or corneal staining

mic gel 1×1 at bedtime (a). Anterior segment photograph at the 3rd week of treatment topical 2% cyclosporine A shows a healed ocular surface without any corneal filaments or corneal staining

there was marked conjunctival hyperemia and limbal vascularization had started. She was diagnosed as early onset pterygium recurrence and the frequency of topical prednisolone acetate was increased to 4×1, with a planned tapering schedule of every 5 days. Topical 0.1% topical cyclosporine A 4×1 was also started. Unpreserved artificial tears 4×1 and the use of sunglasses were advised. At the 12th week visit, limbal vascularization and conjunctival hyperemia were persistent and topical CsA concentration was increased to 2% used 4×1. At the follow-up visit 4 weeks later, vascularization was markedly decreased. Topical 2% cyclosporine A bid was used for 6 months. No recurrence was observed in a 12-month follow-up period (Fig. 4).

Case 4

A 29-year-old female patient applied to our clinic with blurred vision in both eyes. She had a history of bilateral viral conjunctivitis 3 months ago. Visual acuity was 20/30 in her right eye and 20/25 in her left eye. Intraocular pressure was 22 mmHg in both eyes. She had used topical corticosteroid containing eye drops intermittently with recurrence of her symptoms upon cessation of treatment. Biomicroscopic examination revealed bilateral corneal subepithelial infiltrates (Fig. 5a and b). She was given topical loteprednol etabonate 4×1 which was tapered every 5 days and topical 0.1% cyclosporine A 4×1. She was followed up every 2 weeks with no improvement in corneal infiltrates at the 12th week. Topical CsA concentration was increased to 2% and applied 4×1. At

the 4th week, the immune infiltrates were markedly decreased in number and density in both eyes (Fig. 5c and 5d). Visual acuity was 20/20 in both eyes. Maintenance therapy was topical 2% cyclosporine A 2×1 for 6 months. The infiltrates did not show recurrence for a follow-up period of 9 months.

Discussion

Topical CsA, which is an approved and well-known treatment option in dry eye disease appears to be useful for different inflammatory conditions of the ocular surface, as well. Patients with these chronic disorders can avoid prolonged courses of corticosteroids with the addition of topical cyclosporine A to their treatment regimen. Topical use of CsA has been reported to have an excellent safety profile [17]. Clinical trials with topical preparations of 0.05 to 2% for up to 1 year are shown to be safe without serious side effects [18]. Minor side effects, including local burning, stinging and redness may be observed [18]. We also did not observe any serious side effects in our cases, except mild hyperemia and stinging upon instillation of the drug. Clinical signs and symptoms decreased significantly in our patient group and a favorable response to treatment was reported by 83% of the patients.

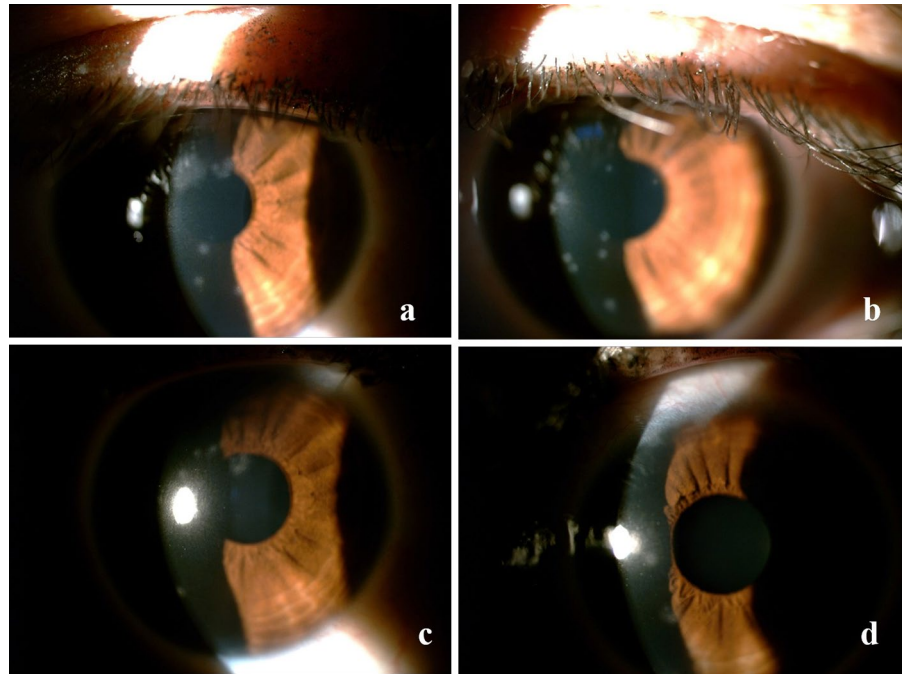
In the current report, indications for the use of topical 2% CsA included pediatric ocular rosacea, filamentary keratitis, adenoviral subepithelial immune infiltrates, early pterygium recurrence and herpetic marginal keratitis. In all these conditions,



Fig. 4 Anterior segment photographs of the left eye of the patient at the 3rd postoperative week after pterygium surgery (a). She was under treatment with topical prednisolone acetate 4×1, topical 0.1% topical cyclosporine A 4×1 and unpreserved artificial tears 4×1 with limited response to treatment.

4 weeks after the initiation of therapy with topical 2% cyclosporine A qid (b), and at the 6th month follow-up (c). Vascularization and hyperemia are markedly decreased during follow-up

Fig. 5 Anterior segment photograph of the patient showing immune sub-epithelial infiltrates in the right and left eyes before (a and b) and after (c and d) 4 weeks of treatment with topical 2% cyclosporine A qid. The immune infiltrates were markedly decreased in number and density in both eyes



inflammation is involved in the pathogenic mechanism leading to morphologic and functional damage to the ocular surface. Innate and adaptive immunity participate to the defensive systems of the ocular surface. Among the innate mechanisms, the activation of toll-like receptors and the increased expression of molecules, such as phospholipase A2 and transglutaminase 2, have been described [19]. The initiation of innate immunity mechanisms via these molecules induces the expression of pro-inflammatory cytokines such as interleukin (IL)-1 α , IL-1 β , IL-6, IL-17, tumor necrosis factor α and matrix metalloproteinases. The expression of these molecules may trigger the consequent activation of the adaptive immune pathways with the accumulation of lymphocytes on the ocular surface, if the irritating stimuli are strong enough or prolonged in time, resulting in a chronic inflammatory condition [19]. In the light of these pathogenic mechanisms, it seems wise to prescribe CsA for long-term treatment of chronic cases where lymphocyte participation and programmed cell death have a relevant role in disease pathogenesis, as in our cases.

Ocular rosacea is an inflammatory disease characterized by meibomian gland dysfunction and blepharo-keratoconjunctivitis, ranging from mild punctate epithelial erosions to severe corneal neovascularization and thinning. Three randomized

controlled studies [20–22] have provided evidence for the effect of topical CsA in ocular rosacea and a Cochrane review [23] concluded that topical cyclosporine was an effective treatment. Although small studies have shown treatment benefits of topical cyclosporine A in pediatric blepharoconjunctivitis, there is a lack of randomized controlled trials on this topic and no standardized outcome measures [24]. Our patient with severe ocular surface inflammation and corneal neovascularization due to ocular rosacea, showed improvement of signs and symptoms with topical 2% CsA. No side effects were observed during a follow-up period of over 12 months.

Filamentary keratitis (FK) is a disorder characterized by the presence of filamentous material composed of epithelial cells and mucin attached to the cornea. The development of FK occurs as a complication of many ocular and systemic diseases and can have severe consequences on vision and quality of life [25]. Although dry eye is the most cited ocular surface disorder that gives rise to filamentary keratitis, other conditions such as exposure keratitis, superior limbic keratoconjunctivitis, corneal edema and ocular surgical procedures such as cataract surgery penetrating keratoplasty and photorefractive keratectomy may lead to FK as well [25]. Similarly, the patients included in the current study had the above

listed underlying diseases leading to FK. Traditional treatments for FK include aggressive lubrication, placement of a bandage contact lens to protect the ocular surface and use of anti-inflammatory agents. However, need for prolonged therapy and recurrences are common. Small studies reported complete resolution of filaments with topical methylprednisolone [26], topical diclofenac [27] and topical 0.05% cyclosporine [28]. In our patient, anti-inflammatory medications, in the form of topical corticosteroids and 0.1% cyclosporine were not effective in improvement of the signs and symptoms. However, the patient showed marked improvement with topical 2% CsA.

Adenoviral keratoconjunctivitis is a very common ocular surface infection and subepithelial infiltrates may be observed in 50% of the patients [29]. These infiltrates are inflammatory in nature and may decrease visual acuity and quality of life. They have been reported to respond well to topical corticosteroids and different concentrations of topical CsA ranging from 0.05 to 2% [30–32]. The infiltrates in our patient decreased with the use of the 2% CsA formulation although it was unresponsive to topical 0.1% CsA.

Recurrence is still the most important complication of pterygium surgery, despite advances in surgical techniques and medications. Conjunctival or limbal autografts, mitomycin C, 5-fluorouracil and anti-vascular endothelial growth factors are used during or after surgery to reduce the rate of recurrence [33]. Topical 0.05% CsA has been reported to be effective in reducing the recurrence rate when used as a postoperative adjuvant treatment [34, 35]. Our patient had an early recurrence which did not respond to 0.1% CsA and could be successfully managed with the use of topical 2% CsA.

The role of topical CsA in the treatment of herpetic stromal keratitis has been studied previously [6, 12, 36]. All these trials reported successful treatment of HSV stromal keratitis with CsA, even in cases unresponsive to topical prednisolone. However, there are no reports evaluating its role in the treatment of herpetic marginal keratitis, as in our case. Although marginal keratitis is an epithelial form of herpetic corneal disease, stromal involvement is also present and anti-inflammatory therapy in addition to antivirals may be needed for complete resolution.

The limitations of the current study are the relatively low number of patients, heterogeneity of ocular pathologies and the lack of washout period before the initiation of 2% CsA. The retrospective nature of the study leads to lack of definitive quantitative data measuring the outcomes related to inflammation. However, our results show that, the 2% CsA formulation may address the needs of different cases with ocular surface inflammation, as a safe option for long-term therapy. It can be used safely with an application regimen up to four times daily. Further controlled studies are required to evaluate the efficacy, optimum dosage, and indications. We believe that preparations including higher concentrations than 0.1% are more effective in similar cases and provide a better overall management of the various forms of ocular surface inflammation.

Authors contribution All authors contributed to the study conception, design, data collection and analysis. The first draft of the manuscript was written by LA, MD and DA, MD commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants or other support were received during the preparation of this manuscript. The authors have no relevant financial or nonfinancial interests to disclose.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval The study was approved by the Institutional Review Board of Baskent University Faculty of Medicine and adhered to the tenets of the Declaration of Helsinki.

Informed consent Informed consent was obtained for the off-label use of topical 2% cyclosporin A from all individual participants included in this retrospective study.

Consent for publication The authors affirm that participants provided informed consent for publication of the images in Figs. 1, 2, 3, 4 and 5.

References

1. Utine CA, Stern M, Akpek EK (2010) Clinical review: topical ophthalmic use of cyclosporin A. *Ocul Immunol Inflamm* 18(5):352–361. <https://doi.org/10.3109/09273948.2010.498657>

2. Donnenfeld E, Pflugfelder SC (2009) Topical ophthalmic cyclosporine: pharmacology and clinical uses. *Surv Ophthalmol* 54:321–338
3. Boboridis KG, Konstas AGP (2018) Evaluating the novel application of cyclosporine 0.1% in ocular surface disease. *Expert Opin Pharmacother* 19:1027–1039
4. Leonardi A, Van Setten G, Amrane M, Amrane M, Ismail D, Garrigue JS et al (2016) Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial. *Eur J Ophthalmol* 26:287–296
5. Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A et al (2010) Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. *Cornea* 29:1392–6
6. Rao SN (2006) Treatment of herpes simplex virus stromal keratitis unresponsive to topical prednisolone 1% with topical cyclosporine 0.05%. *Am J Ophthalmol* 141:771–2
7. Foulks GN (2006) Topical cyclosporine for treatment of ocular surface disease. *Int Ophthalmol Clin* 46:105–122
8. Sacchetti M, Mantelli F, Lambiase A (2014) Systematic review of randomized clinical trials on topical cyclosporine A for the treatment of dry eye disease. *Br J Ophthalmol* 98:1016–1022
9. Baudouin C, Figueiredo FC, Messmer EM, Ismail D, Amrane M, Garrigue JS et al (2017) A randomized study of the efficacy and safety of 0.1% cyclosporine A cationic emulsion in treatment of moderate to severe dry eye. *Eur J Ophthalmol* 27:520–530
10. Doan S, Gabison E, Gatinel D, Duong MH, Abitbol O, Hoang-Xuan T (2006) Topical cyclosporine A in severe steroid-dependent childhood phlyctenular keratoconjunctivitis. *Am J Ophthalmol* 141:62–66
11. Heiligenhaus A, Steuhl KP (1999) Treatment of HSV-1 stromal keratitis with topical cyclosporin A: a pilot study. *Graefes Arch Clin Exp Ophthalmol* 237:435–438
12. Reinhard T, Sundmacher R (1999) Topical cyclosporin A in Thygeson's superficial punctate keratitis. *Graefes Arch Clin Exp Ophthalmol* 237:109–112
13. Hingorani M, Moodaley L, Calder VL, Buckley RJ, Lightman S (1998) A randomized, placebo-controlled trial of topical cyclosporin A in steroid dependent atopic keratoconjunctivitis. *Ophthalmology* 105:1715–1720
14. Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R et al (2002) Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 89:298–303
15. Cetinkaya A, Akova YA, Dursun D, Pelit A (2004) Topical cyclosporine in the management of shield ulcers. *Cornea* 23:194–200
16. Deshmukh R, Ting DSJ, Elshah A, Mohammed I, Said DG, Dua HS (2022) Real-world experience of using cyclosporin-A 0.1% in the management of ocular surface inflammatory diseases. *Br J Ophthalmol* 106(8):1087–1092
17. Pflugfelder SC (2004) Antiinflammatory therapy for dry eye. *Am J Ophthalmol* 137:337–342
18. Kashani S, Mearza AA (2008) Uses and safety profile of cyclosporin in ophthalmology. *Expert Opin Drug Saf* 7:79–89
19. Aragona P (2014) Topical cyclosporine: are all indications justified? *Br J Ophthalmol* 98(8):1001–1002
20. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH (2006) Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. *Cornea* 25:171–175
21. Rubin M, Rao SN (2006) Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis. *J Ocul Pharmacol Ther* 22:47–53
22. Schechter BA, Katz RS, Friedman LS (2009) Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Adv Ther* 26:651–659
23. van Zuuren EJ, Kramer S, Carter B, Graber MA, Fedorowicz Z (2011) Interventions for rosacea. *Cochrane Database Syst Rev* 3:Cd003262
24. Rousta ST (2017) Pediatric blepharokeratoconjunctivitis: is there a “right” treatment? *Curr Opin Ophthalmol* 28:449–453
25. Albietz J, Sanfilippo P, Troutbeck R, Lenton LM (2003) Management of filamentary keratitis associated with aqueous-deficient dry eye. *Optom Vis Sci* 80:420–430
26. Marsh P, Pflugfelder SC (1999) Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. *Ophthalmology* 106:811–816
27. Grinbaum A, Yassur I, Avni I (2001) The beneficial effect of diclofenac sodium in the treatment of filamentary keratitis. *Arch Ophthalmol* 119:926–927
28. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Kornstein HS (2003) Topical cyclosporine A 0.5% as a possible new treatment for superior limbic keratoconjunctivitis. *Ophthalmology* 110:1578–1581
29. Jhanji V, Chan TC, Li EY, Agarwal K, Vajpayee RB (2015) Adenoviral keratoconjunctivitis. *Surv Ophthalmol* 60:435–443
30. Levinger E, Slomovic A, Sansanayudh W, Bahar I, Slomovic AR (2010) Topical treatment with 1% cyclosporine for subepithelial infiltrates secondary to adenoviral keratoconjunctivitis. *Cornea* 29:638–640
31. Okumus S, Coskun E, Tatar MG, Kaydu E, Yayuspayi R, Comez A et al (2012) Cyclosporine a 0.05% eye drops for the treatment of subepithelial infiltrates after epidemic keratoconjunctivitis. *BMC Ophthalmol* 18:12–42
32. Asena L, Şingar Özdemir E, Burcu A, Ercan E, Çolak M, Altınörs DD (2017) Comparison of clinical outcome with different treatment regimens in acute adenoviral keratoconjunctivitis. *Eye* 31(5):781–787
33. Nuzzi R, Tridico F (2018) How to minimize pterygium recurrence rates: clinical perspectives. *Clin Ophthalmol* 12:2347–2362
34. Turan-Vural E, Torun-Acar B, Kivanc SA, Acar S (2011) The effect of topical 0.05% cyclosporine on recurrence following pterygium surgery. *Clin Ophthalmol* 5:881–5
35. Özülken K, Koç M, Ayar O, Hasiripi H (2012) Topical cyclosporine A administration after pterygium surgery. *Eur J Ophthalmol* 22(Suppl 7):5–10
36. Gunduz K, Ozdemir O (1997) Topical cyclosporin as an adjunct to topical acyclovir treatment in herpetic stromal keratitis. *Ophthalmic Res* 29:405–408

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author

self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.