Efficacy of topical cyclosporine 0.05% and osmoprotective lubricating eye drops in treating dry eye disease and inflammation

Ritika Mullick, Sriram Annavajjhala, Prashansa Thakur, Ayushi Mohapatra, Rohit Shetty, Sharon D'Souza

Purpose: To evaluate the effect of topical cyclosporine 0.05% and osmoprotective lubricating eye drops on patients with dry eye disease (DED) with inflammation as measured by raised tear matrix metalloproteinases (MMP-9). Methods: This prospective study included 106 eyes of 53 patients diagnosed with DED based on any of the following DED criteria (Ocular Surface Disease Index [OSDI] score >12, tear film breakup time [TBUT] <10 s, Schirmer’s I test result <10 mm/5 min, ocular surface staining). Ocular surface inflammation was assessed by assessing MMP-9 positivity from tears of the patients in the study (Inflammadry kit Quidel corporation). Patients were prescribed osmoprotective lubricating eye drops (Osmodrops, Cipla Ltd) four times a day and cyclosporine A 0.05% eye drops (Imudrops, Cipla Ltd) twice a day for 6 months. Efficacy of the formulations was evaluated by OSDI scores, Schirmer’s test, TBUT change, reduction in ocular surface staining, and reduction in MMP-9 levels after 6 months of usage. Check P value and add from results Results: After 6 months of topical therapy, improvement was observed in OSDI scores (mean pretreatment: 25.7 ± 12.5, and mean posttreatment: 15.2 ± 8.4), P < 0.001. There was also reduction number of patients who were MMP-9 positive. Out of 75 eyes that tested MMP-9 positive, 70.66% showed reduction in MMP-9 levels (P < 0.0001). Ocular surface staining also improved. Conclusion: Topical osmoprotective lubricating eye drops and cyclosporine A 0.05% reduce inflammation in cases of DED, which correlates with improvement in OSDI scores, ocular surface staining, and reduction in inflammation as measured by levels of tear MMP-9.

Key words: Cyclosporine, dry eye, inflammation, osmoprotection, treatment

Dry eye disease (DED) is a global ocular health issue with increasing number of people affected everyday around the world. It can range from a mildly symptomatic disease to a severe debilitating condition with sight-threatening implications, morbidity, and decreased quality of life.[1] The ocular surface damage encountered in more severe forms of dry eye is largely contributed by the tear film instability and hyperosmolarity, which in turn results in increase in the inflammation on the ocular surface. Tear film hyperosmolarity may result from either reduced aqueous production seen in aqueous-deficient DED and/or increased evaporation seen in the evaporative DED.[2] Evaporative DED is more commonly encountered in clinical practice; however, most cases show a considerable overlap of aqueous-deficient and evaporative DED.[3] In the latter, higher evaporation rates are noted as compared to the normal eye, and this results in increased tear hyperosmolarity even in the absence of tear volume reduction. Many different inflammatory markers have been associated with dry eye including interleukin-1β, IL-6, tumor necrosis factor-α, interferon-γ, and matrix metalloproteinases (MMPs), such as MMP-3 and MMP-9.[4,5] Among the various cytokines, MMP-9 has been known to play a crucial role in initiation and progression of the ocular surface inflammation and forms a target for treatment.[6,7] MMPs are produced in ocular surface diseases and have pathogenic role in corneal ulceration, destruction, and perforation.[8] The levels of MMP-9 have been found to be directly proportional to the severity of dry eye and reduces with an adequate treatment of dry eye.[9] MMP-9 can be measured by various methods like electrophoresis, Western blot assay, enzyme-linked immunoassays, and MMP-9 capture activity measurements.[11,12] The simplest being the clinic based, single-use kit (Inflammadry kit Quidel corporation, San Diego, CA, USA) that measures both active and latent MMP-9.[2,13] The first-line treatment of DED consists of using different artificial tear substitutes like carboxymethylcellulose (CMC), hydroxypropyl methylcellulose 0.3%, and sodium hyaluronate 0.15%. Additives in the tears substitutes like osmoprotectants (glycerine 0.9%, erythritol and L-carnitine) have been found to have additional beneficial effect in the treatment of dry eye disease by balancing the osmotic pressure and protecting cells under extreme osmotic stress.[13] They have been shown to protect corneal epithelial cells from hyperosmolar stress by reducing protein kinases.[16,17] This combination of topical therapy has been shown to have synergistic effects resulting in better tear viscosity and ocular

For reprints contact: WKHLRPedmednow_reprints@wolterskluwer.com

Cite this article as: Mullick R, Annavajjhala S, Thakur P, Mohapatra A, Shetty R, D’Souza S. Efficacy of topical cyclosporine 0.05% and osmoprotective lubricating eye drops in treating dry eye disease and inflammation. Indian J Ophthalmol 2021;69:3473-7.
surface hydration. Controlling the inflammation is key to improving the ocular surface health in DED especially in the more severe forms and can lead to improvement in DED-related symptoms as well. Topical steroids are one of the mainstays in treating ocular surface inflammation; however, long-term use of topical steroids is a major limitation owing to their potential side effects. The use of steroid sparing agents like topical cyclosporine A has been shown to be an effective, safe, and a reliable long-term therapeutic intervention for management of DED. Cyclosporin A has also been reported to decrease the accelerated apoptosis of the epithelial cells in the lacrimal gland and ocular surface that occurs in dry eye.

This study evaluates the effect of a combination of lubricant osmoprotectant eye drops (Osmodrops, Cipla Ltd) with cyclosporine A 0.05% eye drops (Imudrops, Cipla Ltd) in the treatment of DED and associated inflammation.

Methods

This drug interventional, open-label, prospective study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients were explained the nature of the tests to be done and the medications to be used and a written consent was obtained. A total of 106 eyes of 53 patients were included in the study. All patients underwent detailed slit-lamp examination, noncontact tonometry, and dilated fundus examination in addition to dry eye evaluation as part of the routine clinical examination. Patients with mild to moderate aqueous deficiency and evaporative dry eye with two or more of the following criteria were included in the study: Ocular Surface Disease Index (OSDI) > 12, tear break up time (TBUT) between 6 and 10 s; Schirmer’s test I result 8–10 mm/5 min and ocular surface staining. Severity of DED was graded as per the Dry Eye Workshop Study classification.

Patients with severe aqueous deficiency dry eye, meliobian gland dysfunction requiring treatment, cicatrizating causes of ocular surface inflammation (e.g. Stevens Johnson syndrome, ocular cicatricial pemphigoid), active or past history of uveitis, use of chronic topical medications, ocular infections, previous ocular surgery, those already on medications, and use of contact lens were excluded from the study. Patients who did not come for follow-up at the scheduled visit or stopped medications prematurely were excluded from the study. Dry eye examinations were performed in the following sequence: OSDI questionnaire, InflammaDry test, Schimers test, TBUT, and ocular surface staining with fluorescein and in vivo confocal microscopy (IVCM) by Heidelberg Retinal Tomograph 2 Rostock cornea module (Heidelberg engineering, GmBH, Dossenheim, Germany). OSDI is a globally accepted DED assessment tool consisting of 12 questions. The OSDI score ranges from 0 to 100, with higher grading scores implying more severe disease (0–12 is normal, 13–22 mild, 23–32 moderate, and 33–100 severe disease). TBUT assessment was done using a fluorescein dye strip and TBUT was measured on the slit-lamp under cobalt-blue light. The time interval between the patient’s blink and the break in the stained tear film is noted as the TBUT. Schirmer’s test I was done by placing standardized strips in the lateral one-third of the lower eyelid without anesthesia. After 5 min, the length of the wetting of the strips noted. Schirmer’s test with anesthesia was performed by instilling topical anesthetic proparacaine 0.5% eye drops in the eye and repeating the same test with the Schirmer’s strip after dabbing off the excess fluid from the lid margin. The cornea staining score was graded as per the Sjogren’s International Collaborative Clinical Alliance registry ocular examination protocol.

The MMP-9 assessment was done using the InflammaDry assay, which is a visual, qualitative clinic-based test. The sample is collected from the tear meniscus at multiple locations on the lower lid. It is then transferred to the cartridge and read after 10 min. A positive test has a blue and red line in the test window. A test result without a blue line is invalid. IVCM was done before and after using the medications to identify dendritic cell density in the cornea, which is also a marker of inflammation.

All patients were advised to use osmoprotective eye drops (Osmodrops, Cipla Ltd) four times a day and topical preservative free cyclosporine ophthalmic emulsion 0.05% (Imudrops, Cipla Ltd), one drop twice a day in each eye, approximately 12 h apart, as per the international recommendations for the use of cyclosporine in the management of DED. After 6 months, the treatment response was evaluated by repeating the same tests done before starting medications and comparing the values to pretreatment levels.

Statistical analysis

All statistical analysis was performed using the GraphPad 6.0 (GraphPad Software, Inc., La Jolla, CA, USA). The mean value of the individual groups was reported as mean ± SD. A P value of < 0.05 was considered statistically significant.

Results

Patient demographics

A total of 106 eyes of 53 DED patients were included in the study. The mean age was 32.67 ± 11.24 years (range: 21–46 years). There were 25 females and 28 males included. These patients were followed up for a period of 6 months and underwent a repeat clinical assessment of their dry eye status at 6 months.

Clinical parameters of DED

Mean Schirmer’s test value was 11.41 ± 5.32 at 5 min (range 6–30) in DED patients. Mean TBUT of the DED patients was 7.67 ± 3.15 s (range 5–10). Mean OSDI score was 25.7 ± 12.8. Thirty-eight eyes (35.85%) had minimal punctate epithelial erosions (PEEs) inferiorly scored as 1, while 68 eyes (64.15%) did not show any PEEs and were scored as 0 [Fig. 1]. Of the 106 eyes in the 53 DED patients, 70.75% (75 eyes) tested positive for MMP-9 at presentation. Patients with MMP-9 positivity were associated with higher OSDI score with a mean OSDI score among these patients being 29.7 ± 8.1, P = 0.0052. MMP-9 positivity was also significantly associated with decreased Schirmer’s test values, P = 0.0013. The average Schirmer’s level in this group of patients was 9.11 ± 4.41 mm. Patients with lower TBUT were found to have higher OSDI and more MMP9 positivity. P = 0.08 Dendritic cell density is measure on the IVCM. The variation in dendritic cell density was noted, and 73.5% DED eyes were found to have high dendritic cell density on IVCM.
Treatment response

There was an improvement in clinical parameters like the TBUT and ocular surface staining. Mean TBUT of the DED patients improved from 7.67 to 8.15 s ($P = 0.06$), and the percentage of eyes with corneal staining reduced from 35.85% (38 eyes) to 18.87% (20 eyes). There was no statistically significant change in Schirmer’s test values ($P = 0.17$).

Out of 75 eyes that tested MMP-9 positive, 53 eyes (70.66%) showed a negative test after treatment ($P = 2.33706E^{-05}$), while the remaining 22 eyes (29.33%) showed no change in the MMP-9 status posttreatment [Fig. 2a, b]. There was also a reduction in dendritic cell density observed on IVCM [Fig. 3a, b].

There was a significant improvement in the mean OSDI scores of patients on treatment (15.2 ± 8.4 after 6 months compared to 25.7 ± 12.8 at baseline, $P < 0.001$ [Fig. 4].

Discussion

DED is a widely prevalent multifactorial disease of the ocular surface and tear film and has been found to affect 5–40% of adults with increasing prevalence with age and female gender among other risk factors.$^{[22,26,27]}$

Our study had a lower age group of patients with the age range from 21 to 46 years. This has been noted in other studies as well which have shown an increase in the prevalence of DED especially evaporative forms of the disease even among the younger age group.$^{[28,29]}$

This could be related to the increase in computer and digital screen usage in recent times.$^{[30]}$

Multiple studies on DED have shown it to have a higher prevalence among women; however, in our study, there was no significant difference in numbers between males and females. A possible explanation for this could be that this study

Figure 1: Pretreatment punctate epithelial erosions score

Figure 2: (a) Pretreatment MMP 9. (b) Posttreatment MMP 9

Figure 3: (a) Pretreatment high dendritic cell density observed on in vivo confocal imaging. (b) Posttreatment reduction in dendritic cell density observed on in vivo confocal imaging

Figure 4: Change in mean OSDI score posttreatment
included milder cases of aqueous deficient and evaporative dry eye in a younger population and gender preponderance is more associated with older age groups due to the associated hormonal changes.\textsuperscript{31,32}

This study included patients who had mild DED but were still symptomatic with moderate range of OSDI and ocular surface inflammation based on clinical features, MMP-9 positivity, and IVCM dendritic cell changes. Treatment of DED is targeted at restoring the tear volume and quality and reducing the inflammation on the surface.

Studies have shown that inflammation is central to the disease irrespective of the underlying cause and breaking the cycle of inflammation is integral to the treatment of DED. The inflammation of the ocular surface is connected to the hyperosmolarity, tear instability, and apoptosis of the corneal and conjunctival epithelial cells.\textsuperscript{6,36} Hyperosmolarity triggers the release of MMP-9 by various pathways.\textsuperscript{33-35}

In our study, we found a high number of MMP-9 positive as tested by the InflammaDry rapid assay kit in subjects with clinical DED, thereby confirming the inflammatory status of the underlying condition. This finding is similar to results from other studies which have shown that patients with dry eye syndrome (DED) had higher levels of MMP-9 levels as compared to those without and the MMP-9 activity increased proportionally to increasing severity of DED.\textsuperscript{15,23} Hence, the MMP-9 level can be used to monitor treatment response in patients with DED.\textsuperscript{7}

The management of DED is multipronged, with replenishment of tear film, improving the stability of the tear film, and reducing ocular inflammation as its key tenets. It has been shown that the use of topical medications with antiinflammatory properties, such as cyclosporine, corticosteroids, and doxycycline may suppress MMP-9 levels in the tears and decrease apoptosis on the ocular surface.\textsuperscript{38,39} We found similar results in our study, in which we used preservative free cyclosporine A eye drops (Imudrops, Cipla Ltd) as an antiinflammatory agent and analyzed the levels of MMP-9 at 6 months after use of cyclosporine A. We found that there was a statistically significant improvement ($P < 0.01$) in the levels of MMP-9 posttreatment compared to baseline, indicating that topical cyclosporine A 0.05% was beneficial in reducing the underlying inflammation. This also translated to a clinical subjective improvement in patient symptoms as measured by the OSDI scores.

Another important aspect of DED pathogenesis is the tear hyperosmolarity, which results in increased expression and production of proinflammatory cytokines and chemokines. New formulations of artificial tears have been developed that include one or more osmoprotectants like erythritol,\textsuperscript{40} L-carnitine,\textsuperscript{41} which counteract effects of hyperosmotic stress.\textsuperscript{42} Medications that modulate the hyperosmolarity of the ocular surface and topical cyclosporine, which inhibits T cell activation, work synergistically to improve symptoms and signs of dry eye patients with high MMP 9.\textsuperscript{7}

We studied the effect of osmoprotective eye drops (cyclosporine A 0.05\% (Imudrops, Cipla Ltd) in combination with cyclosporine A 0.05\% in this study. Our patients seemed to have benefited from this synergistic combination which is reflected in the overall improvement in the OSDI score, ocular surface staining, and decrease in the MMP-9 levels. This is similar to findings reported in other studies that the use of CMC and osmoprotectants in patients with DED decreased their ocular surface staining.\textsuperscript{43} Increasing severity of the disease or additional problems like meibomian gland dysfunction or underlying systemic disease require multiple modalities of therapy.\textsuperscript{16}

As the patients in this study did not have any significant meibomian gland dysfunction, systemic disease, or severe dry eye-related ocular surface changes, the management did not warrant any additional therapies.

**Limitations of the study**

A larger sample size could give more information regarding the effect of the medications in dry eye. This study evaluates the effect of these medications on mild to moderate grades of dry eye and does not provide any information on their effect in more severe dry eye. Further studies could fill these lacunae.

**Conclusion**

The treatment of DED can be extremely challenging due to the varied subjective symptoms and objective signs with which the patient presents. The inflammation and loss of homeostasis in DED need to be treated to achieve adequate clinical and symptomatic improvement in cases of mild DED. In addition to routine dry eye tests like the Schirmer’s and TBUT, diagnosis can be aided by using tests to detect MMP-9-related inflammation. Medications like osmoprotectants add an extra aspect of protection and treatment over and above the simple lubricating of the ocular surface. This study reinforces the idea that topical cyclosporine 0.05% and osmoprotective lubricants have an important role to play in the management of DED. Additional studies are also warranted in the future with a larger sample and longer follow-up to provide better results.

**Acknowledgements**

This work was supported by an educational grant from Cipla Ltd. None of the authors have any proprietary interest in any medication discussed in this paper.

**Financial support and sponsorship**

This work was supported by an educational grant from Cipla Ltd. None of the authors have any proprietary interest in any medications discussed in this paper.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, et al. TFOS DEWS II report executive summary. Ocul Surf 2017;15:802-12.
2. Bron AJ, Yokoi N, Ga石家 E, Tiffany JM. Predicted phenotypes of dry eye: Proposed consequences of its natural history. Ocul Surf 2009;7:78-92.
3. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: A retrospective study. Cornea 2012;31:472-8.
4. Stevenson W, Chauhan SK, Dana R. Dry eye disease: An immune-mediated ocular surface disorder. Arch Ophthalmol 2012;130:90-100.
5. Chotikavanich S, de Paiva CS, Li de Q, Chen JJ, Bian F, Farley WJ, et al. Production and activity of matrix metalloproteinase-9 on the Indian Journal of Ophthalmology Volume 69 Issue 12

We studied the effect of osmoprotective eye drops (cyclosporine A 0.05\% (Imudrops, Cipla Ltd) in combination with cyclosporine A 0.05\% in this study. Our patients seemed to have benefited from this synergistic combination which is reflected in the overall improvement in the OSDI score, ocular surface staining, and decrease in the MMP-9 levels. This is similar to findings reported
ocular surface increase in dysfunctional tear syndrome. Invest Ophthalmol Vis Sci 2009;50:3203-9.

6. Aragona P, Aggunouz M, Rania L, Postorino E, Sommario MS, Roszkowska AM, et al. Matrix metalloproteinase 9 and transglutaminase 2 expression at the ocular surface in patients with different forms of dry eye disease. Ophthalmology 2015;122:62-71.

7. Park JY, Kim BG, Kim JS, Hwang JH. Matrix metalloproteinase 9 point-of-care immunoassay result predicts response to topical cyclosporine treatment in dry eye disease. Transl Vis Sci Technol 2018;7:31.

8. Stern ME, Pflugfelder SC. Inflammation in dry eye. Ocul Surf 2004;2:124-30.

9. Tseng HC, Lee JT, Lin CC, Chi PL, Cheng SE, Shih RH, et al. IL-1beta promotes corneal epithelial cell migration by increasing MMP-9 expression through NF-kappaB- and AP-1-dependent pathways. PLoS One 2013;8:e57955.

10. Kaufman HE. The practical detection of mmp-9 diagnoses ocular surface disease and may help prevent its complications. Cornea 2013;32:211-6.

11. Brignole F, Pisella PJ, De Saint Jean M, Goldschild M, Goguel A, Baudouin C. Flow cytometric analysis of inflammatory markers in KCS: 6-month treatment with topical cyclosporin A. Invest Ophthalmol Vis Sci 2001;42:90-5.

12. Hulkkonen J, Pertovaara M, Antonen J, Pasternack A, Hurme M, Pollanen P, et al. Matrix metalloproteinase 9 (MMP-9) gene polymorphism and MMP-9 plasma levels in primary Sjögren’s syndrome. Rheumatology (Oxford) 2004;43:1476-9.

13. Schargas M, Ivanova S, Kakkassery V, Dick HB, Joachim S. Correlation of tear film osmolarity and 2 different mmp-9 tests with common dry eye tests in a cohort of non-dry eye patients. Cornea 2015;34:739-44.

14. Sambursky R, Davitt WF3, et al. K, Zhang S, et al.: Dry eye management with osmoprotection and inflammation control. December 2021

15. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. Ocul Surf 2017;15:62-71.

16. Hu X, Su Z, Deng R, Lin J, Li DQ, Pflugfelder SC. Effects of L-carnitine, erythritol and betaine on pro-inflammatory markers in primary human corneal epithelial cells exposed to hyperosmotic stress. Curr Eye Res 2015;40:657-67.

17. Corrales RM, Luo L, Chang EY, Pflugfelder SC. Effects of osmoprotectants on hyperosmolar stress in cultured human corneal epithelial cells. Cornea 2008;27:574-9.

18. Labetoulle M, Chiambaretta F, Shirlaw A, Leoback R, Baudouin C. Osmoprotectants, carboxymethylcellulose and hyaluronic acid multi-ingredient eye drop: A randomised controlled trial in moderate to severe dry eye. Eye (Lond) 2017;31:1512.

19. Razeghinejad MR, Myers JS, Katz LJ. Iatrogenic glaucoma secondary to medications. Am J Med 2011;124:20-5.

20. Zhou QX, Wei RL. Topical cyclosporine A in the treatment of dry eye: A systematic review and meta-analysis. Cornea 2014;33:760-7.

21. Wan KH, Chen LJ, Young AL. Efficacy and safety of topical 0.05% cyclosporine eye drops in the treatment of dry eye syndrome: A systematic review and meta-analysis. Ocul Surf 2015;13:213-25.

22. The epidemiology of dry eye disease: Report of the epidemiology subcommittee of the international dry eye workshop (2007). Ocul Surf 2007;5:93-107.

23. Ocular surface increase in dysfunctional tear syndrome. Invest Ophthalmol Vis Sci 2009;50:3203-9.

24. Whitcker JP, Shiboski CH, Shiboski SC, Heidenreich AM, Kitagawa K, Zhang S, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjogren’s Syndrome International Registry. Am J Ophthalmol 2010;149:405-13.

25. Dysregulated tear fluid nociception-associated factors, corneal dendritic cell density, and vitamin d levels in evaporative dry eye. Invest Ophthalmol Vis Sci 2019;60:2532-42.

26. Acetaminophen and Ibuprofen in the treatment of dry eye disease. Br J Ophthalmol 2014;98:1016-22.

27. Stapleton F, Alves M, Bunya VY, Jallbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf 2017;15:334-65.

28. Shah S, Jani H. Prevalence and associated factors of dry eye: Our experience in patients above 40 years of age at a Tertiary Care Center. Oman J Ophthalmol 2015;8:151-6.

29. Farrand KF, Fride K, Stickland IJ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. Am J Ophthalmol 2017;182:90-8.

30. Dana R, Bradley JL, Gruer A, Pivnery I, Stickland IJ, Evans AM, et al. Estimated prevalence and incidence of dry eye disease based on coding analysis of a large, All-age United States Health Care System. Am J Ophthalmol 2019;202:47-54.

31. Akkaya S, Atakan T, Aikalin B, Aksyos O, Ozkurt Y. Effects of long-term computer use on eye dryness. North Clin Istamb 2018;5:319-22.

32. Tsubota K, Pflugfelder SC, Liu Z, Baudouin C, Kim HM, Messmer EM, et al. Defining dry eye from a clinical perspective. Int J Mol Sci 2020;21:9271.

33. Ahn JH, Choi YH, Paik HJ, Kim MK, Wei WR, Kim DH. Sex differences in the effect of aging on dry eye disease. Clin Interv Aging 2017;12:1331-8.

34. Rhee MK, Mah FS. Inflammation in dry eye disease: How do we break the cycle? Ophthalmology 2017;124:514-9.

35. Corrales RM, Stern ME, De Paiva CS, Welch J, Li DQ, Pflugfelder SC. Desiccating stress stimulates expression of matrix metalloproteinases by the corneal epithelium. Invest Ophthalmol Vis Sci 2006;47:3293-302.

36. Solomon A, Dursun D, Liu Z, Xie Y, Macri A, Pflugfelder SC. Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry-eye disease. Invest Ophthalmol Vis Sci 2006;47:4309-15.

37. Shetty R, Ghosh A, Lim RR, Subramani M, Mishir K, Reshma AR, et al. Elevated expression of matrix metalloproteinase-9 and inflammatory cytokines in keratoconus patients is inhibited by cyclopentolate. Invest Ophthalmol Vis Sci 2015;56:738-50.

38. Pflugfelder SC. Anti-inflammatory therapy of dry eye. Ocul Surf 2003;1:31-6.

39. Foulks GN. Topical cyclosporine for treatment of ocular surface disease. Int Ophthalmol Clin 2006;46:105-22.

40. Kiyosawa K, Zhang S, et al.: Dry eye management with osmoprotection and inflammation control. December 2021