Clinical Ophthalmology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

# Clinical Efficacy and Safety of Preservative Free Cyclosporine in Dry Eye Disease

Aafreen Bari, Aishwarya Dasgupta, Tushar Agarwal, Tanuj Dada, Namrata Sharma

DR. R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

Correspondence: Namrata Sharma, Cataract, Cornea & Refractive Surgery Services, Room 494, Department of Ophthalmology, All India Institute of Medical Sciences, New Delhi, Delhi, 110029, India, Tel +91-11-26593144, Email namrata.sharma@gmail.com

**Abstract:** Dry eye disease (DED) is an ocular surface ailment with a high prevalence in the current era. One of the management principles involves the treatment of the underlying ocular surface inflammation. Topical Cyclosporine therapy is an effective treatment option. However, achieving an adequate drug concentration at the site of action and minimising the associated adverse drug effects, such as stinging and burning sensations at the site of instillation, are the biggest challenges. A preservative-free formulation of Cyclosporine 0.05% (Cyclisis-PF, Intas Pharmaceuticals, India) was studied in 50 patients with mild to moderate DED in a prospective interventional study. Eye drops were prescribed twice daily in addition to conventional treatment. At 12 weeks follow-up, the tear film stability was better in terms of improved tear break up time (TBUT) ($p < 0.01$), non-invasive break up time (NIBUT) ($p < 0.001$), Schirmer's test ($p < 0.01$), lipid layer thickness (LLT) ($p = 0.006$), tear meniscus height (TMH) ($p < 0.01$), corneal staining score ($p < 0.01$), and ocular surface disease index (OSDI) score ($p < 0.01$) at the three-month follow-up. Only five of the 50 (10%) patients had mild adverse drug effects in the form of mild stinging. However, none of the patients discontinued this drug. In conclusion, preservative free cyclosporine is a safe, effective and well tolerated treatment modality in cases of mild to moderate DED.

**Keywords:** Cyclisis-PF, preservative free cyclosporine, dry eye disease

## Introduction

Dry eye disease, also known as keratoconjunctivitis sicca (KCS), is multifactorial. It is characterised by a loss of homeostasis of the tear film and is associated with ocular symptoms, tear film instability, hyperosmolarity, and ocular surface inflammation.[1]

Topical anti-inflammatory agents such as cyclosporine A (CsA) provide a targeted approach to treat and suspend the inflammatory cascade of KCS.[2] Topical cyclosporine was approved by the FDA for the treatment of moderate-to-severe DED in 2003. CsA is a calcineurin inhibitor, which is an activator of T-cells. It prevents T-cell production of inflammatory cytokines and disrupts the immune-mediated inflammatory response.[3,4] CsA is known to reduce DED-induced inflammation associated with corneal and conjunctival epithelium, subconjunctival tissues, and accessory lacrimal glands. Additionally, it increases conjunctival goblet cell density and tear production.[5–8] CsA also binds to cyclophilin D and prevents apoptotic cell death by inhibiting the opening of pores on the mitochondria as a response to cellular stress or damage.[9] Thus, CsA increases the natural production of tears in patients whose tear production is suppressed due to ocular inflammation associated with KCS.

Cyclosporine is known to have poor aqueous solubility. Thus, there are technical challenges for its delivery to the ocular surface. Newer formulations of cyclosporine, like aqueous nano-micellar formulation address few of the delivery challenges and may lessen the time to symptomatic relief, improve tolerability, and enhance patient persistence with the compound. The cationic emulsions and nano-micellar aqueous solutions address formulation, tissue concentration, and drug delivery challenges.

This study was conducted with the aim to evaluate the efficacy and safety profile of a preservative-free aqueous-based ophthalmic formulation of cyclosporine 0.05% in cases with mild-moderate dry eye disease of mixed type.

Received: 30 November 2024
Accepted: 13 March 2025
Published: 31 March 2025

# Methodology

This prospective interventional study assessed the effect of a preservative-free cyclosporine 0.05% formulation in patients with DED. The study was conducted at Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Delhi, India. This study was conducted in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the Institute Ethics Committee (IEC-89/03.03.2023), and CTRI (clinical trial registry, India) registration was performed (CTRI/2024/05/068159).

This study included 50 cases of mild to moderate DED selected from the Dry Eye Clinic at the tertiary eye centre using computer-generated random numbers. Subjects aged ≥18 years who were diagnosed with DED irrespective of sex were included. Cases of DED based on the OSDI ≥18, TBUT ≤10 s, TMH <0.25 mm, Schirmer tear test (without anaesthesia) ≤10 mm/5 min, corneal fluorescein staining score [as per National Eye Institute (NEI) scale] ≥3, conjunctival lissamine green staining score (as per NEI scale) ≥6, Best Corrected Visual Acuity (BCVA) Log MAR equivalent (0.6) or better, normal lid position and closure, and willingness to participate and follow-up as specified in the study were included. Patients with any ocular condition that affects study parameters, such as active ocular infection, ocular inflammation, ocular trauma, blepharitis, or any other condition; unwilling to refrain from contact lens use for the entire duration of this study; any significant illness that could interfere with study parameters; history of any other ocular surgical procedure within 3 months; or a known case of allergy or hypersensitivity to the components of the formulation were excluded.

After providing written informed consent, eligible patients were asked to provide their relevant medical histories and symptoms. Systemic comorbidities were documented, and they underwent detailed slit-lamp examination, dry eye work-up, and fundus evaluation. It included the assessment of ocular signs suggestive of DED, best-corrected visual acuity (BCVA), Schirmer's test, calculation of the ocular surface staining score using sodium fluorescein 1% and Lissamine green, ocular surface analyser (OSA), and assessment of any adverse drug reactions. Patients were followed up at the following points: day 0 (baseline), day 30 (first follow-up), day 60 (second follow-up), and day 90 (third follow-up).

A preservative-free version of cyclosporine 0.05% eye drops, commercially available as Cyclisis PF (Intas Pharmaceuticals Limited, India), was used for this study. Each vial contains 0.5 mg of cyclosporine and an aqueous buffered vehicle QS (preservative). It is a preservative-free, multi-dose, aqueous-based, clear cyclosporine ophthalmic solution (0.05%). Intas Cyclosporine ophthalmic solution (0.05%) was available in a 5 mL pack.

Eye drops were prescribed twice daily for 12 weeks in addition to conventional treatment for DED based on the TFOS DEWS II guidelines.

## Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics software, Version 25.0 (IBM 93 Corp., Armonk, NY). Normality of the data was checked using the Shapiro–Wilk test. All data were parametric and represented in terms of mean and standard deviation. For a comprehensive examination of the data, linear mixed effects models were employed. Clustered data from both eyes of the same patient were combined using robust standard error.[10] The P value was calculated using Post – hoc Bonferroni *t*-test for intra-group comparisons. P value of less than 0.05 was considered statistically significant.

# Results

## Demographic Results

One hundred eyes (50 patients) diagnosed with DED were enrolled in the study, and improvement in DED was assessed using objective parameters at 3 months follow-up. The mean age of patients was 40.8 ± 12.7 years. The study included 27 male patients and 23 females ($p > 0.05$). In the sociodemographic evaluation, 82 percentage of the cases belonged to the urban population, whereas 18 percentage belonged to the suburban area. The majority (76%) of patients belonged to the upper middle class (38/50), while the rest (24%) belonged to the upper class (12/50).

## Clinical Results

The OSDI score improved from 28.719 ± 8.060 to 16.682 ± 9.221 at 3 months follow-up ($p < 0.01$). At 1 and 2 months, there was a significant improvement in the OSDI score ($p < 0.01$).

There was a mean improvement in TBUT from 2.65 ± 1.445 seconds to 5.48 ± 2.290 seconds at three months ($p < 0.01$). At all follow-up periods, there was a statistically significant improvement in the TBUT. Schirmer's score improved from a mean value of 7.00 ± 2.570 mm to 11.26 ± 3.958 mm at 3 months ($p < 0.01$). Statistically significant improvement was observed at each follow-up visit. The LLT increased from the baseline value of 31.65 ± 7.353 nm to 38.40 ± 13.538 nm at 3 months follow-up ($p = 0.006$). At the first- and second-month follow-up, there was an improvement in LLT; however, it reached statistical significance at 3 months follow-up. The TMH increased at the end of 3 months of treatment from a mean value of 0.18890 ± 0.0414 mm to 0.2456 ± 0.0515 mm ($p < 0.01$). The TMH showed a statistically significant improvement at each follow-up visit. The NIBUT improved from 5.024 ± 1.657 s to 5.800 ± 1.618 s ($p < 0.001$) seconds at 3 months follow-up. It showed an improvement in the mean values at all follow-up periods; however, it reached statistical significance at 3 months follow-up. The mean Meibomian losses in the upper and lower lids at baseline were 25.81 ± 5.740% and 16.99 ± 5.905%, respectively. At the end of 3 months, it was 26.01 ± 5.188% and 16.59 ± 5.239%, respectively ($p > 0.05$). There was no change at 3 months follow-up ($p > 0.05$). (Figure 1) The corneal staining score improved from 4.76 ± 1.055 to 2.25 ± 1.708 at 3 months. At each visit, the staining score was significantly higher than that of the previous visit. (Figure 2) All the values are summarized in Table 1.

## Safety Profile

Serious adverse drug events were not observed in any patient. Five patients (10%) experienced mild drug reaction in the form of a slight stinging sensation upon drug instillation. However, none of the patients discontinued this drug. All the patients completed follow-up appointments and continued the use of preservative-free cyclosporine.

# Discussion

DED is a prominent ocular morbidity in developed and developing countries. Its prevalence may be as high as 50%.[11] It is broadly classified into two major types according to the TFOS: aqueous deficient DED and evaporative DED. The chief management principle in cases of DED is restoration of ocular surface health with stabilisation of the tear film. Treatment options include drugs of various classes, such as restoring the aqueous layer (artificial tears, sodium hyaluronate), lipid layer (perfluorohexyloctane ophthalmic solution), mucin layer (diquafosol sodium, rebamipide), anti-inflammatory drugs (cyclosporine), antibiotics, and immunomodulators (Azithromycin and Doxycycline).[12,13] Targeting the underlying inflammation in patients with DED is essential to break the cascade of aetiopathogenesis of DED. Topical

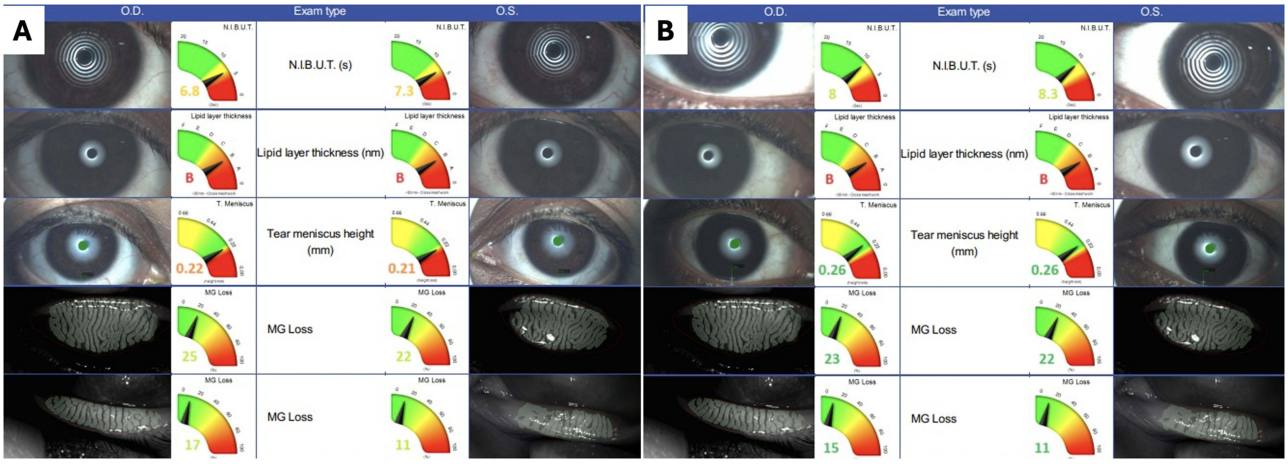


**Figure 1** Representative image of a case shows the improvement in NIBUT, Lipid layer thickness and tear meniscus height of both eyes (**A**) at baseline and (**B**) last follow up (90-day).


https://doi.org/10.2147/OPTH.S505641

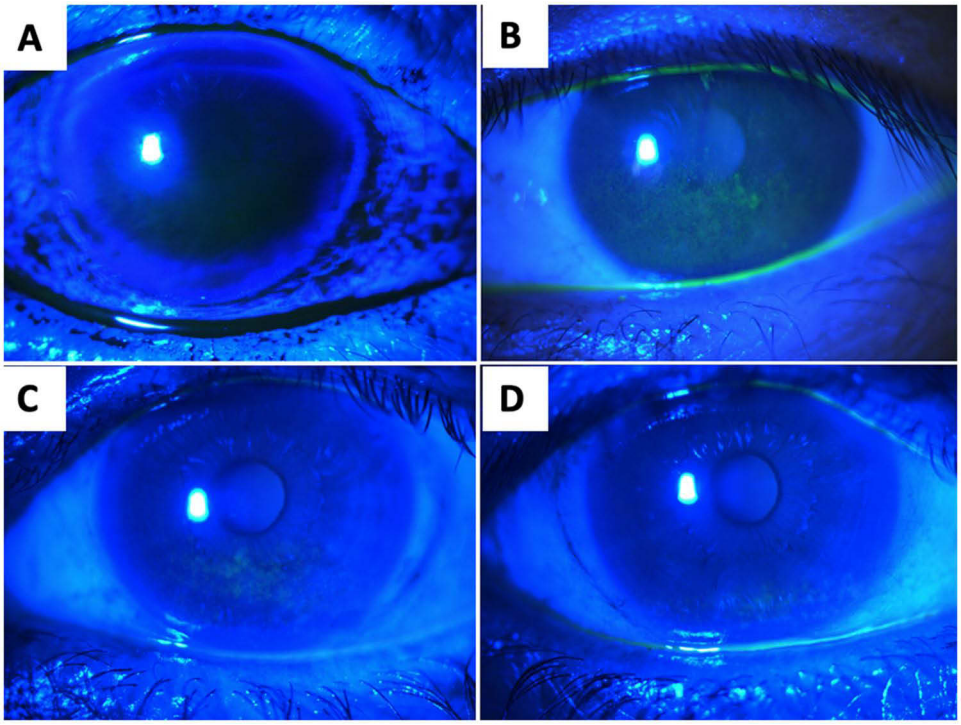


**Figure 2** Representative image of a case shows the improvement in staining score of both eyes from baseline (**A** and **B**) to last follow up (**C** and **D**).

steroids are prescribed for immediate action against ocular surface inflammation, whereas cyclosporine is the drug of choice for a longer sustained action.

In this study, the use of 0.05% preservative-free cyclosporine with novel proprietary lipid (NPL) technology improved OSDI scores at each follow-up visit. It is an assessment of the patient's comfort in being able to perform their daily activities, grade their specific symptoms, and study the impact of surroundings on their eyes. A higher OSDI score implies worse or more severe DED with aggravated symptoms. In this study, the mean OSDI scores were 28.719 ± 8.060 at baseline and 16.682 ± 9.221 at 3 months ($p < 0.01$). This suggests that there was a shift in the mean OSDI from moderate DED (23–32) to mild DED (13–22). There was a significant improvement in the OSDI scores at each follow-up. This shows a consistent improvement in patient comfort and satisfaction with the use of preservative-free 0.05% CsA.[14] A randomized study with a control group may have provided a higher level of evidence. Absence of control group or other available formulations of cyclosporine as controls for comparison is one of the limitations of the study.

**Table 1** Enumerates Various Parameters at Baseline and Subsequent Follow Ups at One, Two and Three months

| Parameter | Baseline (B0) | 1 month (B1) | 2 month (B2) | 3 month (B3) | P value (B0-B3) |
|---|---|---|---|---|---|
| **TBUT** | 2.65 ± 1.445 | 3.53±1.648 | 4.33±1.809 | 5.48±2.290 | < 0.01[#] |
| **Schirmer's Test** | 7.00 ±2.570 | 8.20±3.045 | 9.48±3.249 | 11.26±3.958 | < 0.01[#] |
| **LLT** | 31.65±7.353 | 32.40±8.180 | 34.20±11.095 | 38.40±13.538 | 0.006[#] |
| **TMH** | 0.19 ± 0.04 | 0.21 ± 0.04 | 0.22 ± 0.04 | 0.25 ± 0.05 | < 0.01[#] |
| **NI-BUT** | 5.02 ± 1.65 | 5.32 ± 1.58 | 5.38 ± 1.59 | 5.80 ± 1.62 | < 0.001[#] |
| **Corneal Staining** | 4.76 ± 1.055 | 4.15 ± 1.114 | 3.24 ± 1.577 | 2.25 ± 1.708 | < 0.01[#] |
| **OSDI** | 28.72 ± 8.06 | 26.31 ± 7.62 | 20.90 ± 8.54 | 16.68 ± 9.22 | < 0.01[#] |

**Note**: [#]Post – hoc Bonferroni *t*-test.

LLT improved at all follow-ups and became significantly better than baseline at follow-up in the third month. This indicates that a healthier meibomian gland produces more lipids and improves LLT. Cyclosporine reduces ocular surface inflammation and meibomitis, thereby improving ocular surface health. This also enhances the tear stability. The study showed beneficial effects in terms of improvement in objective tests, such as TBUT, NIBUT, Schirmer's, corneal staining score, and TMH. Cyclosporine is an established drug for the treatment of underlying inflammation in patients with DED. The DEWS-II guidelines suggest that the treatment of this inflammation is essential to break the vicious cycle of DED.[15]

The upper and lower lid meibomian gland losses remained comparable in both groups at the follow-up. This may be due to the permanent damage to the glands at presentation.

Symptomatic improvement in the OSDI score correlated with objective tests like the corneal staining, TMH, LLT, TBUT, NIBUT and Schirmer's test highlight the beneficial role of cyclosporine in cases of DED. Cyclosporine is an anti-inflammatory and immunomodulatory agent that inhibits IL-2 mediated T-cell activation and cytokine production. Additionally, it prevents apoptosis of conjunctival epithelial cells and induces T-cell apoptosis. The drug aids in breaking the cascade of ocular surface inflammation and improves various subjective and objective parameters. It helps in improved tear production and more viable lipid layer, thereby increasing tear film stability.[16] It is often used in addition to ocular lubricants and other treatment modalities like topical steroids, punctal plugs, oral antibiotics and immunomodulatory drugs.

Cyclosporine-A is a cyclic decapeptide drug derived from the submerged fermentation of the aerobic fungus Trichoderma polysporum. The biggest challenge in dispensing this drug is its lipophilic nature, which makes it hydrophobic.[17] It cannot be suspended in an aqueous formulation. The second challenge is the adverse effects associated with the drug. Ocular burning, eye pain, conjunctival hyperemia, discharge, epiphora, foreign body sensation, pruritus, and visual disturbances are known side effects of cyclosporine.[18] These adverse effects are usually so disabling that in up to 60% of cases, they may lead to patient dropout.[19]

Gao et al compared seven formulations of cyclosporine A based on their formula features and percentage of active agents. The various available formulations were discussed on the basis of their composition and formulation.[20] The most popular and FDA-approved formulation Restasis (Allergan Inc., Irvine, CA, United States) is the formulation of cyclosporine 0.05% in an anionic oil-in-water emulsion. However, the greatest challenge associated with its use is its low bioavailability to the ocular surface and the discomfort associated with instillation. Various formulations have been developed to overcome the challenge of achieving adequate drug delivery for cyclosporine-A-like nano-micellar technology.[21] It helps tiny particles penetrate receptor channels.

Cyclisis PF is a cyclosporine 0.05% preservative-free aqueous solution with novel proprietary lipid (NPL) technology. It is a biomimetic natural lipid that enhances the solubility and stabilizes lipophilic CsA in an aqueous base. Upon administration, NPL-based cyclosporine crossed the tear film barrier without compromising the integrity of cyclosporine. At the targeted site of action, the lipid component is washed away along with the tears, leaving cyclosporine on the ocular surface. Thus, it is studied to have enhanced drug bioavailability and improved targeted drug delivery. It helps decrease the time to symptomatic relief and has improved tolerability, as it is formulated at pH 7, which aids in improving drug compliance among patients.

Cyclisis PF is dispensed in a Novelia multidose closing tip system. Thus, there is no need for preservatives in the drug and it prevents bacterial contamination. The non-return valve ensures that no contaminated liquid can be re-introduced into the container after the drop has been dispensed. The intake of air into the Novelia dispenser occurs by a separate venting system with a silicone membrane called PureFlow Technology. The calibrated drops (40μL) mean precise dosing for better treatment adherence.

In conclusion, preservative-free cyclosporine 0.05% with NPL technology is a safe, effective, and preservative-free formulation of an aqueous-based solution that aids in improving drug delivery and clinical outcomes in DED.

## Data Sharing Statement

Data may be shared by the corresponding author upon reasonable request by the reader.

## Funding

This work was supported by the Intas Pharmaceuticals, India.

## Disclosure

All authors report no conflicts of interest for this work.

## References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276–283. doi:10.1016/j.jtos.2017.05.008
2. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II report executive summary. *Ocul Surf*. 2017;15(4):802–812. doi:10.1016/j.jtos.2017.08.003
3. Pflugfelder SC, de Paiva CS. The pathophysiology of dry eye disease: what we know and future directions for research. *Ophthalmology*. 2017;124(11S):S4–S13. doi:10.1016/j.ophtha.2017.07.010
4. Erdinest N, Solomon A. Topical Anti-Inflammatory Agents For Dry Eye Disease. *Harefuah*. 2019;158(2):130–135.
5. Liddicoat AM, Lavelle EC. Modulation of innate immunity by cyclosporine A. *Biochem Pharmacol*. 2019;163:472–480. doi:10.1016/j.bcp.2019.03.022
6. Periman LM, Mah FS, Karpecki PM. A review of the mechanism of action of cyclosporine a: the role of cyclosporine a in dry eye disease and recent formulation developments. *Clin Ophthalmol*. 2020;14:4187–4200. doi:10.2147/OPTH.S279051
7. Schultz C. Safety and efficacy of cyclosporine in the treatment of chronic dry eye. *Ophthalmol Eye Dis*. 2014;6:37–42. doi:10.4137/OED.S16067
8. El Annan J, Chauhan SK, Ecoiffier T, Zhang Q, Saban DR, Dana R. Characterization of effector T cells in dry eye disease. *Invest Ophthalmol Vis Sci*. 2009;50(8):3802–3807. doi:10.1167/iovs.08-2417
9. Lin DT, Lechleiter JD. Mitochondrial targeted cyclophilin D protects cells from cell death by peptidyl prolyl isomerization. *J Biol Chem*. 2002;277(34):31134–31141. doi:10.1074/jbc.M112035200
10. Fan Q, Teo YY, Saw SM. Application of advanced statistics in ophthalmology. *Invest Ophthalmol Vis Sci*. 2011;52(9):6059–6065. doi:10.1167/iovs.10-7108
11. Wróbel-Dudzińska D, Osial N, Stępień PW, Gorecka A, Żarnowski T. Prevalence of dry eye symptoms and associated risk factors among University students in Poland. *Int J Environ Res Public Health*. 2023;20(2):1313. doi:10.3390/ijerph20021313
12. O'Neil EC, Henderson M, Massaro-Giordano M, Bunya VY. Advances in dry eye disease treatment. *Curr Opin Ophthalmol*. 2019;30(3):166–178. doi:10.1097/ICU.0000000000000569
13. Aly Zaky M, Galal Zaky A, Fayez elsawy M, Fatehy Shehata K, Samy Abd Elaziz M. Efficacy of topical azithromycin versus systemic doxycycline in treatment of meibomian gland dysfunction. *J Ophthalmol*. 2023;2023:4182787. doi:10.1155/2023/4182787
14. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol*. 2000;118(5):615–621. doi:10.1001/archopht.118.5.615
15. Rao SK, Mohan R, Gokhale N, Matalia H, Mehta P. Inflammation and dry eye disease-where are we? *Int J Ophthalmol*. 2022;15(5):820–827. doi:10.18240/ijo.2022.05.20
16. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database Syst Rev*. 2019;9(9):CD010051. doi:10.1002/14651858.CD010051.pub2
17. Cholkar K, Gilger BC, Mitra AK. Topical, aqueous, clear cyclosporine formulation design for anterior and posterior ocular delivery. *Transl Vis Sci Technol*. 2015;4(3):1. doi:10.1167/tvst.4.3.1
18. de Oliveira RC, Wilson SE. Practical guidance for the use of cyclosporine ophthalmic solutions in the management of dry eye disease. *Clin Ophthalmol*. 2019;13:1115–1122. doi:10.2147/OPTH.S184412
19. White DE, Zhao Y, Ogundele A, et al. Real-world treatment patterns of cyclosporine ophthalmic emulsion and lifitegrast ophthalmic solution among patients with dry eye. *Clin Ophthalmol*. 2019;13:2285–2292. doi:10.2147/OPTH.S226168
20. Gao D, Da Z, Yang K, Shi Y. Comparison of seven cyclosporine A formulations for dry eye disease: a systematic review and network meta-analysis. *Front Pharmacol*. 2022;13:882803. doi:10.3389/fphar.2022.882803
21. Guo C, Zhang Y, Yang Z, et al. Nanomicelle formulation for topical delivery of cyclosporine A into the cornea: *in vitro* mechanism and *in vivo*permeation evaluation. *Sci Rep*. 2015;5:12968. doi:10.1038/srep12968