Editorial paper

Reumatologia 2024; 62, 6: 395–397
DOI: https://doi.org/10.5114/reum/197334

Topical cyclosporine A in the management of dry eye disease in Sjögren's syndrome

Nora Majtánová, Veronika Kurilová, Petr Kolář

Department of Ophthalmology, Slovak Medical University and University Hospital in Bratislava, Slovakia

The prevalence of dry eye disease varies according to the part of the world, from around 5.28% to 21.7%, with higher occurrence in women, increasing with age and over time [1, 2]. The diagnosis of dry eye disease (DED) is defined as an Ocular Surface Disease Index (OSDI) score of 13 or higher and one of the following signs: a Schirmer's test I score less than or equal to 10 mm, tear break-up time (TBUT) less than or equal to 10 s and a corneal fluorescein staining score of grade 1 or higher [3]. Refractory ocular dryness is defined when the patient does not improve after using a maximum dose of artificial tears and ointments, and other ocular processes, not related to Sjögren's syndrome (SS), e.g. blepharitis, are ruled out. The severity of DED should be defined based on corneal damage and patient symptoms, assessed by the ocular staining score and OSDI [4].

The prevalence of SS in dry-eye patients differs in published studies, ranging from 10% to 28%, with slightly higher occurrence of primary SS [5]. In SS, an immune-mediated aqueous deficient dry eye is present [6]. Because of the immune-base inflammatory component, topical cyclosporine A (CsA) may be the optimal therapeutic option. Cyclosporine A has immunomodulatory actions and regulation of the adaptive immune response. It has the ability to inhibit the activation of T-lymphocytes, together with the inhibition of apoptosis. It is believed that it also inhibits apoptosis of conjunctival epithelial cells, resulting in the improvement of conjunctival goblet cell density. In the topical route of administration its lipophilicity is a challenge; therefore cationic emulsions and nanomicellar aqueous solutions are developed [7]. According to animal studies, sufficient immunomodulatory concentrations are achieved in conjunctiva and cornea, whereas very low concentrations are present in the aqueous humor, vitreous and plasma [8]; therefore systemic side effects are not expected. Topical CsA has been used successfully in many trials for posterior blepharitis, ocular rosacea, post-LASIK dry eye, atopic and vernal keratoconjunctivitis, and in higher concentration also to treat allograft corneal rejection [8]. In this editorial letter, we would like to emphasize the role of topical CsA as an important therapeutic option in patients with SS suffering from DED.

Diagnostic tests of dry eye disease

Besides standard ophthalmologic examination, it is recommended to perform specific tests and questionnaires focused on ocular surface diseases when DED is suspected.

Schirmer test I

The length of the wet part of the standardized Schirmer strip is measured after 5 minutes. Parts of the Schirmer strips are placed in the outer part of the lower fornix under the topical anesthesia and the eyes are closed. A normal result is considered to be 10 mm or more of wet strip.

A length of 5 mm or less fulfills the SS criterion.

Tear break-up time

Tear break-up time is the examination of tear-film stability. After instilling one drop of 1% preservative-free fluorescein solution, the patient blinks several times and stays eye-opened, without blinking. We observe the patient using a blue cobalt filter on the slit-lamp. The time from the last blinking to the tearing of the yellow tear film on the ocular surface is recorded (in seconds). The normal range is from 10 to 35 seconds. For values under 10 seconds, tear instability is suspected.

Corneal staining score

After the instillation of 1% fluorescein solution, we count corneal punctate epithelial erosions and assess the score based on the Oxford scheme (A–E) [3, 9].

Address for correspondence:
Nora Majtánová, Department of Ophthalmology, Slovak Medical University and University Hospital in Bratislava, 11 Antolska St., 851 07, Bratislava, Slovakia, e-mail: nora.majtanova@gmail.com

Received: 22.11.2024; **Accepted:** 28.11.2024

Ocular Surface Disease Index

The OSDI score is the result of the 12-item questionnaire about dry eye symptoms, their effect on vision-related function and environmental triggers. The patient evaluates the statements using 0 (meaning "none of the time") to 4 (meaning "all of the time"). The final score is in the range 0 to 100, where 0–12 is normal, and more than 33 means severe dry eye. The score does not reflect all dry eye symptoms [10].

Therapeutic approaches in dry eye disease in Sjögren's syndrome patients

European Alliance Associations for Rheumatology (EULAR) recommendations for the management of SS recommend the use of artificial eye drops or gels as a first-line therapeutic approach to replace the tear volume, and lubricate and cushion the eye. The dosages should be at least twice daily up to as often as hourly. Artificial tears should be mainly composed of lubricants with a polymeric base or viscosity agent, e.g., methylcellulose and hyaluronate, whereas the use of lubricants with preservatives is in general not recommended, especially when the dose is four or more doses daily. Ophthalmic ointments are recommended to be used before bedtime. Patients with severe DED or who will not respond to lubricants sufficiently will need in addition topical immunosuppressive treatment, or serum eye drops [2].

Topical nonsteroidal anti-inflammatory drugs and glucocorticosteroids (GCs) should be prescribed for short-term use, a maximum of 2–4 weeks, to avoid side effects. Before starting long-term CsA treatment, induction topical GC treatment may be used, especially in eyes with redness, blepharitis, significant tarsal changes and ocular allergy. Another use of topical GCs is for acute flare-ups triggered by immune and environmental factors [4, 11].

Topical CsA at concentration of 0.05% in a twice daily dose has been available since 2002 based on two randomized control trials and most patients preferred this treatment to the treatment using artificial tears. This treatment is safe and well tolerated [12, 13]. Introduction of cationic 0.1% CsA emulsion led to lowering of the dosing interval to once daily [4, 11], and it was proven to be safe and effective in improving signs and symptoms of moderate to severe DED in two multicentric randomized trials (SANSIKA, SICCANOVE) [14].

In contrast, in patients with SS the use of autologous or allogenic serum tear drops is not evidence-based. Their use should be reserved for topical CsA non-responders or intolerant [4].

If all the above-mentioned treatments fail, plug insertion or oral anti-muscarinic agents should be considered [4].

Therapeutic considerations and challenges of topical cyclosporine A

Topical CsA is more effective in DED in patients without SS, compared to patients with SS. In both groups, the Schirmer test score, TBUT, corneal staining and OSDI score improved after 6 and 12 months of treatment. The therapeutic response was less evident in patients with SS, where DED was probably caused by severe systemic inflammatory factors, nor local factors (i.e. qualitative changes in tears and ocular surface) [3, 15].

When discussing the concentration of topical CsA, 0.05% and 0.1% seem to be most appropriate; no additional benefits were observed with higher concentrations [12]. When comparing these concentrations in patients with moderate to severe DED, the treatment reduced superficial punctate keratitis, the OSDI score and patients' symptoms, with the most consistent improvement in objective and subjective findings at 0.1% concentration and greatest reduction of symptoms at 0.05% [12]. In addition, patients with an inadequate response after 0.05% twice daily improved significantly after switching to 0.1% cationic emulsion daily. This was noted after 2 months of treatment in the OSDI index, TBUT, corneal fluorescein staining, corneal sensitivity, and Schirmer test I. However, 29.6% of patients suffered from transient instillation pain, as an adverse effect [16]. Similarly, 29.2% of patients suffered from instillation pain in the SANSIKA study. This could be addressed by the instillation of preservative-free artificial tears 30 minutes before topical treatment.

Planning the duration of the treatment might be strictly individual. In one study the authors initially treated patients with severe dry eye for 6 months with topical 0.05% CsA twice daily, followed by treatment "as needed", which was observed for 10 years. All the patients required prolonged induction treatment (8–41 months), with a median of 20 months. However, the improvement after the initial treatment was sustained for a long time, with few patients requiring additional treatment [17]. These findings may suggest that the topical treatment with topical CsA should be long-term, but not necessarily life-long. Further studies are needed.

Conclusions

Topical CsA is a safe and effective treatment for patients with dry eye with SS. The immunomodulatory mechanism of action of topical CsA predisposes it to reduce the immune-based component of the disease. After 6 months of therapy, improvement of dry eye signs is noticeable. It is available in two concentrations, 0.05% and 0.1%, with the higher one having the advantage of lower dosing – once daily. Clinicians should expect

that treatment efficacy is not as high as in dry eye patients without SS, but it is still an effective treatment option to reduce dry eye signs and achieve symptom relief. The most common side effect is transient instillation pain. Preliminary studies suggest that the treatment with topical CsA should be long-term, but not necessarily life-long. However, our daily clinical practice shows the need for long-term therapy, including bridging with steroids. The need for artificial tears is decreased due to this therapy, but not eliminated.

Disclosures

Conflict of interest: The authors declare no conflict of interest.
Funding: No external funding.
Ethics approval: Not applicable.
Data availability: Not applicable.

References

1. Dana R, Bradley JL, Guerin A, 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, DOI: 10.1016/j.ajo.2019.01.026.
2. Cai Y, Wei J, Zhou J, Zou W. Prevalence and INCIDENCE of Dry Eye Disease in Asia: A Systematic Review and Meta-Analysis. Ophthalmic Res 2022; 65: 647–658, DOI: 10.1159/000525696.
3. Cubuk MO, Ucgul AY, Ozgur A, et al. Topical cyclosporine a (0.05%) treatment in dry eye patients: a comparison study of Sjogren's syndrome versus non-Sjogren's syndrome. Int Ophthalmol 2021; 41: 1479–1485, DOI: 10.1007/s10792-021-01708-1.
4. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis 2020; 79: 3–18, DOI: 10.1136/annrheumdis-2019-216114.
5. Akpek EK, Bunya VY, Saldanha IJ. Sjögren's Syndrome: More Than Just Dry Eye. Cornea 2019; 38: 658–661, DOI: 10.1097/ICO.0000000000001865.
6. Barrientos RT, Godín F, Rocha-De-Lossada C, et al. Ophthalmological Approach for the Diagnosis of Dry Eye Disease in Patients with Sjögren's Syndrome. Life (Basel) 2022; 12: 1899, DOI: 10.3390/life12111899.
7. 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.
8. Donnenfeld E, Pflugfelder SC. Topical ophthalmic cyclosporine: pharmacology and clinical uses. Surv Ophthalmol 2009; 54: 321–338, DOI: 10.1016/j.survophthal.2009.02.002.
9. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003; 22: 640–650, DOI: 10.1097/00003226-200310000-00008
10. Grubbs JR Jr, Tolleson-Rinehart S, Huynh K, Davis RM. A review of quality of life measures in dry eye questionnaires. Cornea 2014; 33: 215–218, DOI: 10.1097/ICO.0000000000000038
11. Retamozo S, Baldini C, Bootsma H, et al. Therapeutic Recommendations for the Management of Older Adult Patients with Sjögren's Syndrome. Drugs Aging 2021; 38: 265–284, DOI: 10.1007/s40266-021-00838-6.
12. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. Ophthalmology 2000; 107: 967–974, DOI: 10.1016/s0161-6420(00)00035-x.
13. Gao M, Zhao L, Liang R, et al. Evaluation of the Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops (II) in the Treatment of Dry Eye Associated with Primary Sjögren's Syndrome. Ocul Immunol Inflamm 2023; 31: 1662–1668, DOI: 10.1080/09273948.2022.2094812.
14. Baudouin C, Figueiredo FC, Messmer EM, et al. 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 2017; 27: 520–530, DOI: 10.5301/EJO.5000952.
15. Fujita M, Igarashi T, Kurai T, et al. Correlation between dry eye and rheumatoid arthritis activity. Am J Ophthalmol 2005; 140: 808–813, DOI: 10.1016/j.ajo.2005.05.025.
16. Chan YH, Sun CC. Efficacy and safety of topical cyclosporine 0.1% in moderate-to-severe dry eye disease refractory to topical cyclosporine 0.05% regimen. Taiwan J Ophthalmol 2023; 13: 68–74, DOI: 10.4103/tjo.TJO-D-22-00140.
17. Straub M, Bron AM, Muselier-Mathieu A, Creuzot-Garcher C. Long-term outcome after topical ciclosporin in severe dry eye disease with a 10-year follow-up. Br J Ophthalmol 2016; 100: 1547–1550, DOI: 10.1136/bjophthalmol-2015-306930.