Different Clinical Applications of Topical Cyclosporine in Ophthalmology: Review for Ophthalmologists

Aplicações Clínicas da Ciclosporina Tópica em Oftalmologia: Revisão para Oftalmologistas

Fernando Faria-Correia[1-5 *], Sara Ribeiro[1-4], Rui Silva[2], Álvaro Silva[2], Carlos Cruz[2], Christophe Pinto[2], Marina João[2], Jorge Vasco Costa[2], Bernardo T. Lopes[5,6-9], Joana Mello Amaral[6-7], Faride W. Tanos[6-7], Marcella Q. Salomão[6-8], Sandra Rodrigues-Barros[5,10,11], Pedro Baptista[5,12], Nuno Franqueira[3,6], José Carlos Mendes[3], Tiago Monteiro[1-4], Fernando Vaz[1,3,4], Renato Ambrósio Jr[5-8,13]

[1] Serviço de Oftalmologia, CUF Porto, Porto, Portugal
[2] Oftalconde, Porto, Portugal
[3] Serviço de Oftalmologia, Hospital de Braga, Braga, Portugal
[4] School of Medicine, University of Minho, Braga, Portugal
[5] Rio de Janeiro Corneal Tomography and Biomechanics Study Group
[6] VisareRio, Rio de Janeiro, Brazil
[7] Instituto de Olhos Renato Ambrósio, Rio de Janeiro, Brazil
[8] Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil
[9] School of Engineering, University of Liverpool, Liverpool, United Kingdom
[10] Serviço de Oftalmologia, Hospital Garcia da Orta, Almada, Lisboa, Portugal
[11] Serviço de Oftalmologia, CUF Almada e CUF Cascais, Portugal
[12] Serviço de Oftalmologia, Centro Hospitalar Universitário do Porto, Porto, Portugal
[13] Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, Brazil

Received/Recebido: 2021-02-17
Accepted/Aceite: 2021-02-22
Published/Publicado: 2021-02-31

ABSTRACT

Cyclosporine A (CsA) is an immunomodulatory agent that has a selective inhibitory action on T-cell lymphocytes. Topical CsA with various formulations has been used in ophthalmology. This article aims to present a review of the published scientific literature reviewed by peers and to illustrate some applications of CsA in the areas of ocular surface diseases.

KEYWORDS: Administration, Ophthalmic; Cyclosporine/therapeutic use; Dry Eye Syndromes/drug therapy; Eye; Ophthalmic Solutions

RESUMO

A ciclosporina A (CsA) é um agente imunomodulador que apresenta uma ação inibtória selectiva sobre os linfócitos células T. O CsA tópico com várias formulações tem sido usado na Oftalmologia. Este artigo tem como objetivo apresentar uma revisão da literatura científica publicada revisada por pares e ilustrar algumas aplicações da CsA na áreas das doenças da superfície ocular.

PALAVRAS-CHAVE: Administração Oftálmica; Ciclosporina/uso terapêutico; Olho; Síndromes do Olho Seco; Soluções Oftálmicas

INTRODUCTION

In the early 1970s, cyclosporine (CsA) was discovered as an antifungal cyclic undecapeptide agent derived from the fungi *Tolypocladium inflatum* and *Beuveria* nevus.[1,2] Its immunosuppressive action has been very extensively analyzed and was described in 1976, especially due to its widespread use in some medical conditions. CsA (Fig. 1) was the first immunosuppressive agent that allowed selective and relatively safe immunoregulation of T-cell lymphocytes. For instance, it was used in solid organ transplantation in order to reduce the incidence of graft rejection.3 In this scientific review, the authors describe the distinct mechanisms of action of CsA, different ophthalmic formulations available in the market, and clinical indications in Ophthalmology based on clinical studies or trials, with a special focus on anterior segment conditions.

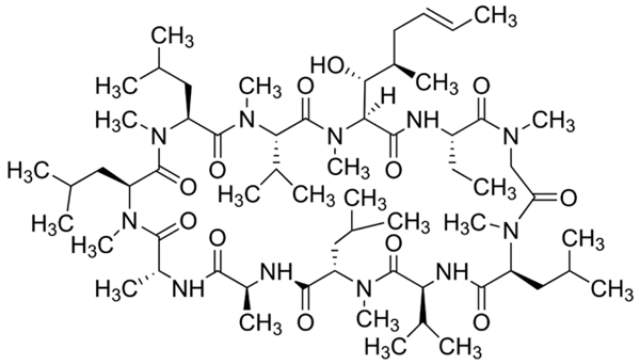

Figure 1 - Molecular structure of cyclosporine A

CELLULAR EFFECTS OF CYCLOSPORINE

The mechanisms of action of CsA are assisted by two cytoplasmic proteins designated by cyclophilins (type A and type D), which are peptidylprolyl-isomerases featuring chaperonic action on misfolded proteins.[4] By binding to these cytoplasmatic proteins, CsA acts as a calcineurin inhibitor, which blocks T-cell lymphocytes activation.[5,6] on the other hand, it also presents an antiapoptotic effect.[7]

Cyclosporine-cyclophilin A complex

This complex is responsible for the inhibition of T-cell lymphocyte activation by inhibiting the activity of the serine/threonine phosphatase calcineurin.[4] Calcineurin normally dephosphorylates the nuclear factor for T-cell lymphocyte activation (NF-AT) in the cytoplasm due to the increase intracellular calcium levels, which is a repercussion of an antigen-binding to the T-cell receptor presented on the surface. At a nuclear level, dephosphorylated NF-AT enhances the transcription of several genes that participate in T-cell activation process, such as interleukin (IL).[2] Secreted IL-2 binds to its receptors on the T-cell surface, promoting cell division by a self-propagating system.[8,9] Other scientific studies suggest this pathway is involved in cytokine and chemokine production by eosinophils and mast cells in the allergic response, but is also presented among other types of cells.[4,10]

Cyclosporine-cyclophilin D complex

This complex is thought to be primarily responsible for apoptosis inhibition.[4] The main action of this complex is to prevent the opening of the mitochondrial permeability transition (MPT) pores.[11,12] In response to cellular stress, these types of pores open and different mitochondrial proteins are released from the intermembrane space, such as cytochrome C and nucleases. For instance, the cytochrome C activates a cascade of caspases that are apoptosis-specific proteases.[12,13] Interestingly, scientific reports also described that calcineurin inhibition by the cyclosporine-cyclophilin A complex may contribute to the apoptosis inhibition effect. This pathway might interfere with the activation of BAD, which is a proapoptotic protein anchored to the outer mitochondrial membrane.[4,14]

CURRENT PHARMACOLOGIC FORMULATIONS

In 2003, the Food and Drug Administration (FDA) approved an ophthalmic emulsion of 0.05% CsA (Restasis®; Allergan, Inc., Irvine, CA, USA) to increase tear film production in patients with dry eye syndrome. This drug presents a preservative-free anionic oil-in-water formulation that includes castor oil with glycerin, polysorbate-80 and carbomer copolymer with sodium hydroxide (to adjust the pH of the solution).[15-17]

In 2015, a cationic nanoemulsion of CsA (Ikervis®; Santen SAS, Evry, France) had been approved by the European Medical Agency (EMA) for patients with dry eye syndrome. In a multicentric randomized trial, this formulation significantly reduced the incidence of superficial punctacte keratitis in patients with dry eye syndrome during a six months follow-up period.[18-20]

Another formulation (OTX-101 0.09%; CEQUA™; CsA 0.09%; Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA) was also approved by the FDA in 2018 to increase tear production in patients with dry eye syndrome. This drug presents nanomicellar components that encapsulate hydrophobic CsA within their hydrophilic cores. This particular feature promotes solubility and dispersion of the drug into the tear film. Regarding this formulation, CsA has traditionally been formulated as an oil-based preparation due to its high lipophilicity and poor water solubility. However, oil-based solutions often have poor tolerability and low bioavailability. Since CsA has a lipophilic nature, this molecule has a higher affinity for an oil-based vehicle than for the target tissues. As a result, an aqueous delivery approach pretends to increase the drug's bioavailability of and reduce its adverse effects.[21-26]

SAFETY PROFILE AND SIDE EFFECTS

The use of topical CsA is associated with an inferior incidence of complications compared to long-term use of corticosteroids. The latter is associated with increased intraocular pressure and subcapsular cataract development. The safety profile for topical CsA in clinical studies was very favorable.[16,17,27,28] In 2000, multicenter and randomized studies reported the efficacy and safety of CsA ophthalmic emulsion in moderate to severe dry eye disease. For example, 25.3% (74/293) of the patients treated with CsA 0.05% ophthalmic emulsion reported adverse effects. The most prevalent complaints were burning eyes and foreign-body sensation (14.7% and 13.1%, respectively). Ocular discharge and hyperemia were reported in 3.1% and 2.0%, respectively. Interestingly, the outcomes suggested that the immunosuppressive effect of topically CsA 0.05% did not affect the protective capacity of the ocular surface against infection.[29]

Regarding the systemic absorption, a very sensitive high-performance liquid chromatography (HPLC) tandem-mass spectroscopy analysis detected CsA in only six blood samples (310 samples in total) from patients receiving the 0.1% formulation. Nevertheless, no CsA was detected in any blood samples from patients who instilled CsA 0.05% ophthalmic emulsion.[29]

With the most recent formulations, the reported side effects were also similar. For example, in a phase 3 study involving the cationic emulsion of CsA (Ikervis®; Santen SAS, Evry, France), the patients in the emulsion group experienced instillation discomfort compared to the vehicle group (29.2% and 8.9%, respectively). In the clinical trials with the cationic nanoemulsion of CsA and the OTX-101 0.09%, 10% and 3.5% discontinued the study during the follow-up, respectively, due to mild to moderate adverse effects (resolved without treatment).[20,23,25]

CLINICAL INDICATIONS IN OPHTHALMOLOGY

DRY EYE SYNDROME

Dry eye syndrome (*keratoconjunctivitis sicca*) is one of the most prevalent ophthalmic diseases. Epidemiological reports performed worldwide have described a prevalence of dry eye that can range from 5% to 50%, depending on the study population and diagnostic criteria. Distinct risk factors for dry eye disease have been identified. People with dry eye syndrome typically report foreign-body sensation, ocular burning or photophobia. Vision-related complaints, such as blurred or fluctuating vision, may also be referred by the patients. The Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) presented an evidence-based definition of dry eye syndrome in recognition of its multifactorial nature. This ocular surface disease features a loss of the tear film homeostasis, and the consequent tear film instability and hyperosmolarity, ocular surface inflammation and neurosensorial irregularities, which have essential etiological roles in the visual symptoms presented by the patients.[17,30]

TFOS DEWS II recommends a stepwise therapeutic approach, starting with education, dietary modification, eyelid hygiene and ocular lubricants. Topical CsA was introduced to increase tear film production in patients with dry eye disease refractory to these conservative approaches, especially ocular lubrification. Nevertheless, due to the chronic and progressive behavior of this ocular surface condition, CsA is also prescribed in less severe patients.[17,28,31]

As mentioned previously, tear film hyperosmolarity plays an essential role in the vicious cycle of the disease. Based on these practice patterns, tear osmolarity threshold values varied from 305 mOsm/L to 316 mOsm/L.[33-35] A crucial point to answer the variability of the threshold values is tear film instability, which is a hallmark feature of the condition. For example, mild, moderate, and severe dry eyes had average tear osmolarity values of approximately 302+/-8 mOsm/L, 315+/-10 mOsm/L, and 336+/022 mOsm/L, respectively.[36] Another point that is also implied on the variability in threshold values is the distribution of the severity of the disease in distinct populations. Interestingly, the effect of anti-inflammatory medication, such as topical CsA, on tear film osmolarity was less evident in previous reports due to methodological limitations, such as small sample size, lack of a control group, and randomization.[30,35]

Previous studies described that molecular markers are related to cell apoptosis, such as CD40, caspase or Fas-ligand, which are up-regulated in the conjunctival epithelial cells of dry eye patients. Distinct cytokines [(IL-1α, IL-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β)] are also in elevated level in the tear film and ocular surface of patients with dry eye syndrome.[30,31,37] Conjunctival biopsies from these subjects submitted to treatment with topical CsA for 6 months revealed a significant reduction in IL-6 expression, suggesting that production of pro-inflammatory cytokines in the ocular surface may be reduced by treatment with topical CsA.[38] Another inflammatory marker presented and well correlated with clinical signs and symptoms is the matrix metalloproteinase-9 (MMP-9).[39] Park et al concluded that MMP-9 grading can be used to predict the ocular surface status and monitor the therapeutic response. In this study, MMP-9–positive patients responded more favorably to topical CsA than did MMP-9–negative patients. With impression cytology, squamous metaplasia of the conjunctival epithelium can be identified in dry eye patients.[40] A previous study described a normalizing effect on CsA therapy on conjunctival squamous metaplasia and increased conjunctival goblet cell density.[31]

Ocular Rosacea is often misdiagnosed, which may lead to long inflammatory processes with significant visual consequences for affected patients, from inflammation of the eyelid margin and blepharitis to severe corneal involvement (for example, corneal ulcers, infiltrates, pannus).[41] A previous study suggested that ocular signs of rosacea may influence meibomian gland morphology and function, causing meibomian gland atrophy or loss. Bilgin et al reported a significant improvement in ocular signs and symptoms after treatment. Interestingly, there was an increase in Schirmer test and break-up time scores in patients that

CsA therapy.[43]

The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study sought to determine the incidence of dry eye and its severity in patients undergoing cataract surgery and to assess the signs and symptoms of dry eye in this patient population. This was a prospective, multicenter, observational study of 136 patients, at least 55 years of age (mean patient age was 70.7 years.), who were scheduled to undergo cataract surgery. Almost 60% had never complained of a foreign body sensation; only 13% complained of a foreign body sensation half or most of the time. The majority of patients (62.9%) had a tear break-up time ≤5 seconds, 77% of eyes had positive corneal staining, and 50% of the eyes had positive central corneal staining. Eighteen percent had Schirmer's score with anesthesia ≤5 mm. The authors concluded that the incidence of dry eye in patients scheduled to undergo cataract surgery in a real-world setting is higher than anticipated. This ocular surface condition can be exacerbated by cataract surgery procedure.[44]

CONTACT LENS INTOLERANCE

These patients can present some dry eye clinical signs, such as the decrease in the tear film production and in tear film break-up time. Previous studies also demonstrated that contact lens wearers presented increased IL-6 levels in the tear film and decreased goblet cell density in the ocular surface.[45,46] The parallelism of clinical and histopathophysiology findings between dry eye syndrome and contact lens intolerance indicates that topical CsA could be a practical approach for these patients.[47] A previous randomized study evaluated the adequacy of topical CsA 0.05% (one drop twice per day) in patients with contact lens intolerance. This 5-week, randomized, investigator-masked study enrolled 17 patients with self-reported contact lens–related dryness. Changes from baseline in fluorescein staining of the cornea and conjunctiva and in tear break-up time were used to determine the improvement of dry eye. Clinical symptoms were assessed by lens wear time, use of rewetting drops during lens wear, subjective evaluation of dryness, and the completion of the Ocular Surface Disease Index questionnaire. The results suggest that this therapeutic approach may be helpful in this type of patient. For instance, contact lens wear time improved by an average of 1.9 hours per day in patients treated with topical CsA. After five weeks, patients using CsA showed statistically better improvements in temporal bulbar conjunctival fluorescein staining.[47]

OCULAR ALLERGIC DISEASE

Eosinophils and mast cells play an essential role in allergic ocular pathology, which leads to the stimulation and stromal infiltration of T-cell lymphocytes. For example, high levels of TNF-α and IFN-γ were described in the tear film of patients with atopic keratoconjunctivitis.[48-50] These conditions feature a long-standing inflammation of the ocular surface, which may induce conjunctival scarring and corneal complications (such as, shield ulcer and corneal pannus), especially in patients with vernal keratoconjunctivitis.[48,51] Topical CsA is an option to be considered for patients that need a long-term treatment regimen.[52-54] Concerning the effects on a histological level, superior tarsal conjunctival biopsies demonstrated a decreased number of activated T-cell lymphocytes in the stroma after this therapeutic approach.[55] The treatment with topical CsA also revealed interesting clinical results in distinct clinical trials. In this sense, a randomized, double-masked, placebo-controlled study analyzed the efficacy and safety of CsA in patients with chronic atopic keratoconjunctivitis. The results demonstrated that CsA 0.05% therapy can help patients with steroid-resistant atopic keratoconjunctivitis. The slit-lamp findings related to this condition also improved during the follow-up compared to the placebo group. Another double-masked, placebo-controlled clinical trial included 20 patients with vernal keratoconjunctivitis and studied the effect of CsA 2% in preservative-free artificial tears during a 22 weeks follow-up period. One month later, the CsA therapy helped significantly reduce the clinical findings and symptoms related to the condition.[56]

LASER-ASSISTED IN SITU KERATOMILEUSIS (LASIK) INDUCED NEUROTROPHIC EPITHELIOPATHY (LNE)

During LASER vision correction procedures, the corneal nerves are transected (in LASIK) or pruned (in photorefractive keratectomy - PRK), resulting in a loss of the homeostasis-maintaining feedback loop of the lacrimal functional unit. The diagnosis of LNE is based on clinical symptoms and signs related to ocular surface irritation, such as ocular fatigue, burning, itching, foreign body sensation, fluctuating vision, dryness, eyelids heaviness and photophobia.[57,58] This ocular surface condition usually improves as corneal reinnervation takes place, returning to preoperative baseline by about 9 to 12 months after LASIK. The method of LASIK flap creation can make a difference regarding the incidence of postoperative dry eye syndrome. In one study, the incidence of LNE and the need for aggressive postoperative treatments was significantly lower in eyes that had femtosecond flaps compared with eyes that had microkeratome flaps.[59] Regarding small-incision lenticule extraction (SMILE), this laser vision correction procedure was also demonstrated to reduce the neurotrophic impact on the cornea.[60] Based on the literature review, topical CsA can be recommended as preoperative and postoperative therapy for patients that present or are at risk of developing dry eye syndrome. A randomized, double-masked trial included 21 patients who underwent bilateral LASIK for myopia correction and compared artificial tears and topical CsA 0.05%. Regarding the latter group, patients were instructed to start the treatment 1 month before the surgery, was discontinued for the first 48 hours after the procedure, and then resumed for the following 3 months. The postoperative tear film production evaluated by Schirmer´s test was statistically higher in the CsA group during the following 6 months after the procedure. This clinical trial also demonstrated a greater refractive postoperative predictability in patients who underwent CsA therapy.[61]

OTHER OCULAR SURFACE CONDITIONS

Graft-versus-host disease (GVHD) often affects the lacrimal glands, the conjunctiva, the lids, the cornea, and the remaining ocular surface. Some related ocular problems include dry eye syndrome, ocular surface scarring, cicatricial lagophthalmos, persistent corneal epithelial defects or melting.[62] The main therapeutic aim in the management of ocular GVHD is the treatment of inflammation and dryness to relieve patients' symptoms and to maintain ocular integrity and function.[62,63] Malta et al evaluated the efficacy of topical CsA 0.05% in treating dry eye syndrome related to GVHD after bone marrow transplantation of hematopoietic stem cells.[64] In this study, 81 patients received topical CsA starting 1 month before bone marrow transplantation (treatment group) and 24 patients did not receive CsA until at least 6 months after the transplantation (control group). The authors concluded that initiation of topical CsA before the transplantation might decrease the inflammatory response in the lacrimal glands, which may be responsible for dry eye syndrome. The results demonstrated that symptoms related to this condition were significantly more severe in the control group at 3 months, 1 year, and 2 years. In a series of five clinical cases of chronic GVHD patients with different severity degrees of ocular surface disease (diffuse punctate epithelial erosions to sterile corneal melting), topical CsA 0.1% was added to the treatment regimen, and the evolution of the ocular disease was recorded. This therapeutic approach showed to be an appropriate modality in managing ocular surface abnormalities in these patients.64

Topical CsA may also be considered to treat ocular complications related to Stevens-Johnson syndrome (SJS). This condition is potentially fatal characterized by widespread skin necrosis and epidermal detachment, with a reported mortality rate of 1%-5%. The pathological mechanisms are attributed to keratinocyte death derived from Fas-ligand binding and cytotoxic T-lymphocytes cells. CsA can be an effective approach for this condition, once it inhibits T cell-lymphocyte activation. Acute ocular inflammation can be reported in 43%-81% of patients and up to 35% of them may experience permanent visual loss.[65] Previous studies assessed the efficacy of topical CsA 0.05% in patients with SJS or ocular cicatricial pemphigoid who had a chronic dry eye. For instance, thirty cases of SJS patients who developed dry eye defined by symptoms and signs, including the Schirmer I test, the fluorescein clearance test (FCT), and corneal staining (fluorescein and Rose Bengal staining) were treated with CsA 0.05% eye drops twice daily for 6 months. Seventeen patients (56.67%) completed the study. However, eight patients (26.67%) withdrew from the study as a result of the side effects related to CsA topical therapy (pain, redness, and eyelid swelling during instillation). All 17 subjects demonstrated significant improvement in dry eye symptoms, conjunctival injection, corneal staining, Schirmer I test, and FCT (p<0.05). The authors concluded that topical CsA 0.05% can be beneficial in the treatment of chronic dry eye associated with SJS.[66,67]

Another ocular condition in which CsA may be beneficial is in the chronic treatment of sequelae associated with herpes simplex virus (HSV) keratitis.[68] Host cell interactions with HSV trigger an inflammatory cascade with activated T-cell lymphocytes cells, which is responsible not only for clearance of virus but also for progressive corneal opacification due to inflammatory cell infiltration, angiogenesis, and corneal nerve loss.[68] Ocular herpes simplex infection and its complications continue to cause significant visual burden and decreased quality of life.[69] Once topical corticosteroids might be required for a long period to control this condition, topical CsA can be considered a treatment option in this group of patients.[70] Peyman et al compared topical CsA 2% eye drop with prednisolone acetate 1% eye drop for the treatment of herpetic stromal keratitis (HSK) in a randomized clinical trial. Thirty-eight eyes of 33 patients with HSK were randomly assigned to receive either 2% Cs-A or 1% prednisolone acetate eye drops. All subjects received oral acyclovir 400 mg twice a day. Both topical regimens demonstrated to be effective for the treatment of HSK. For example, the authors described that within-group analysis there was a significant improvement of total cornea optical density after 30 days of treatment in both groups (30.3± 10.5 to 28.3± 9.8, $p < 0.001$ for prednisolone group, and 30.5± 8.8 to 28.8± 8.3 $p < 0.001$ for Cs-A group, mean ± SD). The best-corrected visual acuity also significantly improved in both groups.[71] In a prospective clinical report, 12 patients were treated with CsA 0.05% combined with topical prednisolone in a tapering regimen. After 3 months of topical CsA, corneal inflammation signs decreased, with a mean time of 3.8 weeks to treat the stromal keratitis. Corneal vascularization that was present before initiation of CsA treatment regressed in 7 patients.[72]

Different studies evaluated the efficacy of topical CsA treatment in patients with subepithelial corneal infiltrates (SEI). These corneal findings may be a source of significant visual impairment, justifying the use of various therapeutic approaches. In a prospective study, 37 eyes of 22 patients with SEI after adenoidal keratoconjunctivitis were treated with topical CsA 0.5% with a specific regimen (first administered at 4 drops per day for 15 days, then at a rate of 2 drops per day for a variable period ranging from 15 days to 6 months). After treatment, the slit-lamp examination revealed a marked decrease in the number and density of SEI from the 15th day. No ocular complications or side effects were observed during the 13 months of follow-up.[73]

Another indication for topical CsA regimen could be as adjuvant therapy after pterygium surgery. Several studies revealed that CsA 0.05% can be used safely and effectively after this procedure to obtain lower rates of recurrence.[74] Zhnag et al evaluate the efficacy and tolerability of CsA as an adjuvant treatment for primary pterygium surgery. Seven studies were included in this meta-analysis. The data showed that adjuvant use of CsA could significantly reduce the risk of pterygium recurrence compared with pterygium excision alone.[75]

Patients who were unilateral long-standing prosthetic eye (over a period of 5 years) were enrolled in a 5-month follow-up study. The authors analyzed the effects of topical CsA 0.05% in patients with ocular discomfort resulting from long-standing prosthetic eye wearing. Ocular symptoms improved after 1 month of treatment in all patients. Slit-lamp examination showed no statistically significant difference in the tear meniscus and eyelid margin inflammation. The Schirmer´s test also improved after 3 months of therapy.[76]

CONCLUSION

The immunosuppressive action of CsA was described in 1976 and has been used as a systemic immunomodulatory drug in specific medical conditions, due to its selective and relatively safe immunoregulation of T-cell lymphocytes. Scientific reviews revealed that distinct ocular surface diseases, such as dry eye syndrome, present activated T-cells lymphocytes and pro-inflammatory mediators, which play an essential role in the lacrimal unit's dysfunction. Since the inflammatory process is implicated in this type of ocular disease, the immunomodulation action of topical CsA has proved to be a valuable therapeutic option during the last decades. Several studies reported that CsA was effective in patients with contact lens intolerance, LNE, and ocular allergic diseases, especially in those clinical cases refractory to other treatments or prolonged corticosteroids regimens. Although the use of topical CsA is widespread, de Paiva et al identified the need for robust, well-planned, long-term, and more extensive clinical trials with established reporting guidelines to minimize bias and better evaluate the efficacy of CsA during long-term follow-up.[77]

ETHICAL DISCLOSURES

Conflicts of Interest: Dr Ambrósio is consultant for Alcon, Zeiss and Oculus; Dr Faria-Correia and Dr Monteiro are consultants for Alcon; Dr Lopes receives research funds from Oculus.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Dr. Ambrósio é consultor da Alcon, Zeiss e Oculus; Dr. Faria-Correira e Dr. Monteiro são consultores da Alcon; Dr. Lopes recebe fundos de investigação da Oculus

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

REFERENCES

1. Borel JF, Feurer C, Magnee C, Stahelin H. Effects of the new anti-lymphocytic peptide cyclosporin A in animals. Immunology. 1977;32:1017-25.
2. Bushley KE, Raja R, Jaiswal P, Cumbie JS, Nonogaki M, Boyd AE, et al. The genome of tolypocladium inflatum: evolution, organization, and expression of the cyclosporin biosynthetic gene cluster. PLoS Genet. 2013;9:e1003496.
3. Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev. 2006:CD005161.
4. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology. 2000;47:119-25.
5. Fruman DA, Klee CB, Bierer BE, Burakoff SJ. Calcineurin phosphatase activity in T lymphocytes is inhibited by FK 506 and cyclosporin A. Proc Natl Acad Sci U S A. 1992;89:3686-90.
6. Halloran PF, Kung L, Noujaim J. Calcineurin and the biological effect of cyclosporine and tacrolimus. Transplant Proc. 1998;30:2167-70.
7. Waldmeier PC, Zimmermann K, Qian T, Tintelnot-Blomley M, Lemasters JJ. Cyclophilin D as a drug target. Curr Med Chem. 2003;10:1485-506.
8. Du S, Hiramatsu N, Hayakawa K, Kasai A, Okamura M, Huang T, et al. Suppression of NF-kappaB by cyclosporin a and tacrolimus (FK506) via induction of the C/EBP family: implication for unfolded protein response. J Immunol. 2009;182:7201-11.
9. Ames P, Galor A. Cyclosporine ophthalmic emulsions for the treatment of dry eye: a review of the clinical evidence. Clin Investig. 2015;5:267-85.
10. Matsuda S, Moriguchi T, Koyasu S, Nishida E. T lymphocyte activation signals for interleukin-2 production involve activation of MKK6-p38 and MKK7-SAPK/JNK signaling pathways sensitive to cyclosporin A. J Biol Chem. 1998;273:12378-82.
11. Li Y, Johnson N, Capano M, Edwards M, Crompton M. Cyclophilin-D promotes the mitochondrial permeability transition but has opposite effects on apoptosis and necrosis. Biochem J. 2004;383:101-9.
12. Gao J, Sana R, Calder V, Calonge M, Lee W, Wheeler LA, et al. Mitochondrial permeability transition pore in inflammatory apoptosis of human conjunctival epithelial cells and T cells: effect of cyclosporin A. Invest Ophthalmol Vis Sci. 2013;54:4717-33.
13. Green DR, Kroemer G. The pathophysiology of mitochondrial cell death. Science. 2004;305:626-9.
14. Wang HG, Pathan N, Ethell IM, Krajewski S, Yamaguchi Y, Shibasaki F, et al. Ca2+-induced apoptosis through calcineurin dephosphorylation of BAD. Science. 1999;284:339-43.
15. Lallemand F, Furrer P, Felt-Baeyens O, Gex-Fabry M, Dumont JM, Besseghir K, et al. A novel water-soluble cyclosporine A prodrug: ocular tolerance and in vivo kinetics. Int J Pharm. 2005;295:7-14.
16. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. Ophthalmology. 2007;114:76-9.
17. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15:276-83.
18. Agarwal P, Rupenthal ID. Modern approaches to the ocular delivery of cyclosporine A. Drug Discov Today. 2016;21:977-88.
19. Boboridis KG, Konstas AGP. Evaluating the novel application of cyclosporine 0.1% in ocular surface disease. Expert Opin Pharmacother. 2018;19:1027-39.
20. Pisella PJ, Labetoulle M, Doan S, Cochener-Lamard B, Amrane M, Ismail D, et al. Topical ocular 0.1% cyclos-

porine A cationic emulsion in dry eye disease patients with severe keratitis: experience through the French early-access program. Clin Ophthalmol. 2018;12:289-99.
21. Vaishya RD, Khurana V, Patel S, Mitra AK. Controlled ocular drug delivery with nanomicelles. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014;6:422-37.
22. Cholkar K, Gilger BC, Mitra AK. Topical, aqueous, clear cyclosporine formulation design for anterior and posterior ocular delivery. Transl Vis Sci Technol. 2015;4:1.
23. Tauber J, Schechter BA, Bacharach J, Toyos MM, Smyth-Medina R, Weiss SL, et al. A Phase II/III, randomized, double-masked, vehicle-controlled, dose--ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease. Clin Ophthalmol. 2018;12:1921-9.
24. Karpecki PM, Weiss SL, Kramer WG, O'Connor P, Evans D, Johnston J, et al. A phase 1, open-label, single-arm study evaluating the ocular safety of OTX-101 and systemic absorption of cyclosporine in healthy human volunteers. Clin Ophthalmol. 2019;13:591-6.
25. Mandal A, Gote V, Pal D, Ogundele A, Mitra AK. Ocular Pharmacokinetics of a Topical Ophthalmic Nanomicellar Solution of Cyclosporine (Cequa(R)) for Dry Eye Disease. Pharm Res. 2019;36:36.
26. Weiss SL, Kramer WG. Ocular Distribution of Cyclosporine Following Topical Administration of OTX-101 in New Zealand White Rabbits. J Ocul Pharmacol Ther. 2019;35:395-402.
27. Gumus K, Mirza GE, Cavanagh HD, Karakucuk S. Topical cyclosporine A as a steroid-sparing agent in steroid-dependent idiopathic ocular myositis with scleritis: a case report and review of the literature. Eye Contact Lens. 2009;35:275-8.
28. de Oliveira RC, Wilson SE. Practical guidance for the use of cyclosporine ophthalmic solutions in the management of dry eye disease. Clin Ophthalmol. 2019;13:1115-22.
29. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology. 2000;107:631-9.
30. Periman LM, Perez VL, Saban DR, Lin MC, Neri P. The Immunological Basis of Dry Eye Disease and Current Topical Treatment Options. J Ocul Pharmacol Ther. 2020;36:137-46.
31. 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;14:4187-200.
32. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15:438-510.
33. Szalai E, Berta A, Szekanecz Z, Szucs G, Modis L, Jr. Evaluation of tear osmolarity in non-Sjogren and Sjogren syndrome dry eye patients with the TearLab system. Cornea. 2012;31:867-71.
34. Versura P, Campos EC. TearLab(R) Osmolarity System for diagnosing dry eye. Expert Rev Mol Diagn. 2013;13:119-29.
35. Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. Clin Ophthalmol. 2015;9:2039-47.
36. Bunya VY, Pistilli M, Ying GS. Progressively Increased Variation in Tear Osmolarity Mirrors Dry Eye Severity--Reply. JAMA Ophthalmol. 2015;133:1482.
37. Iwata M, Soya K, Sawa M, Sakimoto T, Hwang DG. CD40 expression in normal human cornea and regulation of CD40 in cultured human corneal epithelial and stromal cells. Invest Ophthalmol Vis Sci. 2002;43:348-57.
38. Hessen M, Akpek EK. Dry eye: an inflammatory ocular disease. J Ophthalmic Vis Res. 2014;9:240-50.
39. 39. Messmer EM, von Lindenfels V, Garbe A, Kampik A. Matrix Metalloproteinase 9 Testing in Dry Eye Disease Using a Commercially Available Point-of-Care Immunoassay. Ophthalmology. 2016;123:2300-8.
40. 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.
41. Arman A, Demirseren DD, Takmaz T. Treatment of ocular rosacea: comparative study of topical cyclosporine and oral doxycycline. Int J Ophthalmol. 2015;8:544-9.
42. Machalinska A, Zakrzewska A, Markowska A, Safranow K, Wiszniewska B, Parafiniuk M, et al. Morphological and Functional Evaluation of Meibomian Gland Dysfunction in Rosacea Patients. Curr Eye Res. 2016;41:1029-34.
43. Bilgin B, Karadag AS. Effects of combined oral doxycycline and topical cyclosporine treatment on ocular signs, symptoms, and tear film parameters in rosacea patients. Arq Bras Oftalmol. 2018;81:466-70.
44. Trattler WB, Majmudar PA, Donnenfeld ED, McDonald MB, Stonecipher KG, Goldberg DF. The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study: the effect of dry eye. Clin Ophthalmol. 2017;11:1423-30.
45. Schultz CL, Kunert KS. Interleukin-6 levels in tears of contact lens wearers. J Interferon Cytokine Res. 2000;20:309-10.
46. Cakmak SS, Unlu MK, Karaca C, Nergiz Y, Ipek S. Effects of soft contact lenses on conjunctival surface. Eye Contact Lens. 2003;29:230-3.
47. Hom MM. Use of cyclosporine 0.05% ophthalmic emulsion for contact lens-intolerant patients. Eye Contact Lens. 2006;32:109-11.
48. Foster CS, Rice BA, Dutt JE. Immunopathology of atopic keratoconjunctivitis. Ophthalmology. 1991;98:1190-6.
49. Metz DP, Hingorani M, Calder VL, Buckley RJ, Lightman SL. T-cell cytokines in chronic allergic eye disease. J Allergy Clin Immunol. 1997;100:817-24.
50. Oray M, Toker E. Tear cytokine levels in vernal keratoconjunctivitis: the effect of topical 0.05% cyclosporine a therapy. Cornea. 2013;32:1149-54.
51. 51. Westland T, Patryn EK, Nieuwendaal CP, van der Meulen IJE, Mourits MP, Lapid-Gortzak R. Vernal shield ulcers treated with frequently installed topi-

cal cyclosporine 0.05% eyedrops. Int Ophthalmol. 2018;38:363-8.
52. Keklikci U, Dursun B, Cingu AK. Topical cyclosporine a 0.05% eyedrops in the treatment of vernal keratoconjunctivitis - randomized placebo-controlled trial. Adv Clin Exp Med. 2014;23:455-61.
53. Yucel OE, Ulus ND. Efficacy and safety of topical cyclosporine A 0.05% in vernal keratoconjunctivitis. Singapore Med J. 2016;57:507-10.
54. Chatterjee A, Bandyopadhyay S, Kumar Bandyopadhyay S. Efficacy, safety and steroid-sparing effect of topical cyclosporine A 0.05% for vernal keratoconjunctivitis in indian children. J Ophthalmic Vis Res. 2019;14:412-8.
55. Vichyanond P, Kosrirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. Curr Allergy Asthma Rep. 2013;13:308-14.
56. Kilic A, Gurler B. Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. Can J Ophthalmol. 2006;41:693-8.
57. Wilson SE. Laser in situ keratomileusis-induced (presumed) neurotrophic epitheliopathy. Ophthalmology. 2001;108:1082-7.
58. Wilson SE, Ambrosio R. Laser in situ keratomileusis--induced neurotrophic epitheliopathy. Am J Ophthalmol. 2001;132:405-6.
59. Salomao MQ, Ambrosio R, Jr., Wilson SE. Dry eye associated with laser in situ keratomileusis: Mechanical microkeratome versus femtosecond laser. J Cataract Refract Surg. 2009;35:1756-60.
60. Reinstein DZ, Archer TJ, Gobbe M, Bartoli E. Corneal sensitivity after small-incision lenticule extraction and laser in situ keratomileusis. J Cataract Refract Surg. 2015;41:1580-7.
61. Kanellopoulos AJ. Incidence and management of symptomatic dry eye related to LASIK for myopia, with topical cyclosporine A. Clin Ophthalmol. 2019;13:545-52.
62. Dietrich-Ntoukas T, Cursiefen C, Westekemper H, Eberwein P, Reinhard T, Bertz H, et al. Diagnosis and treatment of ocular chronic graft-versus-host disease: report from the German-Austrian-Swiss Consensus Conference on Clinical Practice in chronic GVHD. Cornea. 2012;31:299-310.
63. Westekemper H, Scholz SL, Thomasen H, Halfwassen C, Steuhl KP. Ocular graft versus host disease : Corneal complications . Ophthalmologe. 2017;114:697-702.
64. Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A, et al. Treatment of ocular graft-versus--host disease with topical cyclosporine 0.05%. Cornea. 2010;29:1392-6.
65. Lee HY, Fook-Chong S, Koh HY, Thirumoorthy T, Pang SM. Cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis: Retrospective analysis of a cohort treated in a specialized referral center. J Am Acad Dermatol. 2017;76:106-13.
66. Prabhasawat P, Tesavibul N, Karnchanachetanee C, Kasemson S. Efficacy of cyclosporine 0.05% eye drops in Stevens Johnson syndrome with chronic dry eye. J Ocul Pharmacol Ther. 2013;29:372-7.
67. Branisteanu DC, Stoleriu G, Branisteanu DE, Boda D, Branisteanu CI, Maranduca MA, et al. Ocular cicatricial pemphigoid (Review). Exp Ther Med. 2020;20:3379-82.
68. 68. Valerio GS, Lin CC. Ocular manifestations of herpes simplex virus. Curr Opin Ophthalmol. 2019;30:525-31.
69. Lobo AM, Agelidis AM, Shukla D. Pathogenesis of herpes simplex keratitis: The host cell response and ocular surface sequelae to infection and inflammation. Ocul Surf. 2019;17:40-9.
70. Khan BF, Pavan-Langston D. Clinical manifestations and treatment modalities in herpes simplex virus of the ocular anterior segment. Int Ophthalmol Clin. 2004;44:103-33.
71. 71. Peyman A, Nayebzadeh M, Peyman M, Afshari NA, Pourazizi M. Topical cyclosporine-A versus prednisolone for herpetic stromal keratitis: a randomized controlled trial. Acta Ophthalmol. 2019;97:e194-e8.
72. Rao SN. Treatment of herpes simplex virus stromal keratitis unresponsive to topical prednisolone 1% with topical cyclosporine 0.05%. Am J Ophthalmol. 2006;141:771-2.
73. Zghal I, Fekih O, Zgolli HM, Chargui S, Malek I, Nacef L. Cyclosporin A eye drop and subepithelial adenoviral keratoconjunctivitis infiltrates. Tunis Med. 2019;97:639-43.
74. 74. Ozulken K, Koc M, Ayar O, Hasiripi H. Topical cyclosporine A administration after pterygium surgery. Eur J Ophthalmol. 2012;22 Suppl 7:S5-10.
75. Zhang Q, Bao N, Liang K, Tao L. Adjuvant Use of Cyclosporine A in the Treatment of Primary Pterygium: A Systematic Review and Meta-Analysis. Cornea. 2018;37:1000-7.
76. Han JW, Yoon JS, Jang SY. Short-term effects of topical cyclosporine A 0.05% (Restasis) in long-standing prosthetic eye wearers: a pilot study. Eye. 2014;28:1212-7.
77. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. Cochrane Database Syst Rev. 2019;9:CD010051.

Corresponding Author/
Autor Correspondente:

Fernando Faria Correia
Avenida do Bessa
Edifício Boapor II, 216, 7º Frente
4100-012 Porto, Portugal
f.faria.correia@gmail.com

ORCID: 0000-0002-8824-7862