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Uses of Topical Cyclosporine in Ophthalmology: A Review

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ABSTRACT

Topical cyclosporine A (CsA) has emerged as an effective treatment for various ocular surface diseases, particularly in managing inflammation-related conditions like dry eye disease (DED), allergic eye disorders, and post-surgical complications. This review synthesizes the current literature on the use of topical CsA in ophthalmology, highlighting its efficacy, safety, and potential applications. Key studies demonstrate that topical CsA, including formulations such as 0.05% CsA and newer cationic emulsions, significantly improves symptoms and clinical parameters in DED, reducing ocular inflammation and enhancing tear production. It is also beneficial in refractive surgery and cataract surgery, where it accelerates recovery and alleviates post-operative dry eye symptoms. In addition to DED, topical CsA has shown promise in treating other ocular inflammatory conditions, such as vernal keratoconjunctivitis, atopic keratoconjunctivitis, and pterygium, particularly in steroid-resistant cases. While CsA is well-tolerated and effective, its use in preventing corneal graft rejection and managing other chronic ocular inflammations requires additional research to confirm its long-term benefits. Overall, topical CsA represents a versatile, non-invasive option for managing a wide range of ocular inflammatory conditions, offering a safe and effective treatment alternative for many patients.

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HISTORY OF CYCLOSPORINE

Cyclosporine A (CsA) was first isolated from the fungus Tolypocladium inflatum and was discovered in 1972 by researchers at Sandoz in Switzerland.[1] Its immunosuppressive properties were identified in 1976, leading to further immunological studies and research into its structure and synthesis.[2]

MECHANISM OF ACTION

Calcineurin is a calcium/calmodulin-dependent serine-threonine protein phosphatase. When activated, calcineurin dephosphorylates regulatory sites on several transcription factors, particularly nuclear factor of activated T-lymphocytes (NFATs).[3] Cyclosporine A (CsA) functions as a calcineurin inhibitor, modulating the immune response by blocking T cell infiltration, activation, and the release of inflammatory cytokines including IL-2 and IL-4.[4,5,6,7] Additionally, CsA inhibits p38 and JNK activation, which are involved in IL-2 production.[8] It inhibits mitochondrial permeability transition pore opening, Fas/Fas ligand upregulation, and caspase activation hence inhibiting apoptosis.[9]

REVIEW

A literature review was performed to extract relevant information from databases like Pubmed, MedLine, Google Scholar and Cochrane Library. The keywords used for extracting the articles such as “cyclosporine”, “topical cyclosporine”, “allergic eye disorders”, “dry eye disease”, “corneal graft”, “keratitis”, “keratoconjunctivitis”, “corneal refractive surgery” and “cataract surgery” were combined using Boolean logic operations. Titles, abstracts, and full-text articles were screened and scrutinized for their information.

Topical cyclosporine for Dry Eye Disease

According to the report of the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), published in 2017 "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[10] In general, treatment of dry eye disease includes topical lubricants with or without preservatives, topical corticosteroid therapy, topical immunosuppressive agents, and punctal occlusion with temporary or permanent plugs.

The reduction in inflammation, achieved through the inhibition of T-cell activation and the down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland[11,12] is believed to improve tear production.[13,14] Topical cyclosporine also enhances goblet cell density and reduces epithelial cell apoptosis.[15] Commercially available topical cyclosporine 0.05% (Restasis, Allergan, Irvine, CA, USA) and 1% compounded preparations are commonly used to treat various inflammatory ocular surface disorders.[16] For patients with severe dry eye disease who do not respond to the standard twice-daily regimen, increasing the frequency of topical cyclosporine application may offer greater effectiveness.[17,18]

0.05% Cyclosporine in dry eye disease

In a systematic review by Kelvin H. Wan et al., the safety and efficacy of 0.05% topical cyclosporine in treating dry eye syndrome (DES) were evaluated. This review included 12 randomized-controlled trials with 1367 patients. Compared to controls, patients using 0.05% cyclosporine eye drops exhibited lower Ocular Surface Disease Index scores, longer tear film breakup times, improved Schirmer I scores, reduced corneal fluorescein staining, and higher goblet cell densities. Overall, twice-daily application of 0.05% cyclosporine eye drops significantly improved both objective and subjective outcomes in DES patients.[19]

Wenhao Xu et al.[20] and Ha Rim So et al.[21] reported significant reductions in inflammatory factor levels and matrix metalloproteinase-9 (MMP-9) expression, respectively, following the use of 0.05% cyclosporine A.

0.1% Cyclosporine in dry eye disease

Yuan-Hsi Chan et al. conducted a retrospective study to assess the efficacy and safety of 0.1% cyclosporine A cationic emulsion (CsA CE) on 23 patients who underwent prior treatment with 0.05% cyclosporine A anionic emulsion (CsA AE) in moderate to severe dry eye disease (DED) but had insufficient response. Dry eye parameters assessed included tear break-up time (TBUT), corneal fluorescein staining (CFS), corneal sensitivity, Schirmer's test without anesthetics, and the Ocular Surface Disease Index questionnaire. After 2 months of treatment with 0.1% CsA CE, significant improvements were observed in CFS ($P < 0.001$), corneal sensitivity ($P = 0.008$), and TBUT ($P = 0.01$).[22]

Similar improvement was seen by Wiktor Stopyra who conducted a prospective study to assess the efficacy of 0.1% cyclosporine A (CsA) cationic emulsion (CE) in the treatment of dry eye disease (DED) in terms of ocular surface disease index (OSDI).[23]

Similarly, Esen K. Akpek et al. conducted a vehicle-controlled clinical trial (ESSENCE-2 trial) with 834 participants. They confirmed that treatment with a water-free 0.1% cyclosporine solution resulted in early therapeutic improvements in the ocular surface compared to the vehicle control.[24] David L. Wirta et al. performed ESSENCE-2 Open-Label Extension study which demonstrated sustained efficacy of water-free, non-preserved 0.1% topical cyclosporine ophthalmic solution over one year for both signs and symptoms of DED, with the treatment proving safe and well-tolerated over the long term.[25]

Ines Lanzl et al. conducted a prospective study involving 236 patients to evaluate the effectiveness, tolerability, and safety of 0.1% cyclosporine A (CsA) cationic emulsion (CE) in routine clinical practice for treating severe keratitis and dry eye disease (DED). Follow-ups at weeks 4, 12, and 24 and month 12, revealed significant reductions in CFS (Corneal fluorescein staining) scores, eyelid and conjunctival erythema, and subjective ocular symptoms. Tolerability was rated as "satisfactory," "good," or "very good" by 97.2% of physicians and 95.7% of patients.[26] A similar non-randomized clinical trial by Laura Valencia-Nieto et al. on 20 subjects[27] and a prospective study by Gerd Geerling et al. involving 472 adults yielded comparable results.[28]

Cyclosporine A loaded contact lens

Jonghwa Kim et al. developed a cellulose acetate phthalate-based pH-responsive contact lens (CL) loaded with cyclosporine A (CsA-CL). CsA was released continuously from the CsA-CL at physiological conditions (37°C, pH 7.4) without an initial burst and remained stable under storage conditions (4°C, pH 5.4) for up to 90 days. Safety assays showed normal ranges for cytotoxicity, ocular irritation, visible light transmittance, and oxygen permeability. CsA concentrations

in the conjunctiva, cornea, and lens increased over time and were most effective in the CsA-CL group, with significant improvements in tear volume, TBUT, corneal fluorescein staining, conjunctival goblet cell density, and corneal apoptotic cell counts compared to other groups.[29]

Intense pulsed light (IPL) therapy combined with 0.05% topical cyclosporine A

Yanan Huo et al. conducted a prospective randomized trial with 60 participants to evaluate the effectiveness and safety of intense pulsed light (IPL) therapy combined with 0.05% topical cyclosporine A (CsA) eye drops for treating Sjögren's Syndrome-related dry eyes (SS-DE). Participants were randomized to receive either 0.1% sodium hyaluronate (Group S) or 0.05% CsA (Group C) eye drops plus IPL therapy. Group C exhibited greater increases in Ocular Surface Disease Index (OSDI), noninvasive tear breakup time (NBUT), meibomian gland expressibility, and meibum quality, with significant improvements in Schirmer I test and lid margin abnormalities compared to Group S. [30]

There may be an increase in non-serious, treatment-related adverse effects (particularly burning) in the CsA group. In summary, newer formulations of cyclosporine like cyclosporine cationic emulsion, water free cyclosporine and micellar nano-particulate (MNP) cyclosporine emulsion have shown to be useful in treating dry eye disease and also as an adjunct to the conventional treatment. Cellulose acetate phthalate-based pH-responsive contact lens (CL) loaded with cyclosporine A and intense pulsed light (IPL) therapy combined with 0.05% topical cyclosporine A (CsA) eye drops are some newer ways where cyclosporine is used topically as treatment for dry eye disease.

Topical cyclosporine after refractive surgery

Gholam A. Peyman et al. conducted a prospective, randomized, single-center clinical study involving 44 eyes from 22 patients scheduled for bilateral LASIK surgery. One eye of each patient was randomly assigned to receive cyclosporine drops twice daily for 3 months in addition to standard postoperative LASIK medication. Corneal sensitivity was measured using the Cochet-Bonnet esthesiometer in various locations around and within the LASIK flap before the surgery and at 1 day, 1 week, 1 month, and 3 months after the procedure. The study found that cyclosporine significantly improved corneal sensitivity at 3 months post-LASIK, indicating that topical cyclosporine enhances corneal nerve regeneration.[31]

Roxana Ursea et al. conducted a retrospective study involving 85 eyes to compare the recovery of uncorrected visual acuity (UCVA) following LASIK in patients treated with topical 0.05% cyclosporine A (49 eyes) versus those treated with a standard postoperative regimen (36 eyes). UCVA was measured at 1 week, 1 month, and 3 months postoperatively. The use of cyclosporine A was associated with a better and faster recovery of UCVA.[32]

Anastasios John Kanellopoulos performed a prospective study involving 145 eyes (82 female, 63 male) that developed clinically significant dry eye within 1 month after LASIK and were treated with cyclosporine A. A control group (group B) with no dry eye symptoms was matched for age and gender. The study assessed Schirmer's test, tear film break-up time (TBUT), and Ocular Surface Disease Index (OSDI) questionnaire, along with central corneal epithelial thickness (CET) and topographic epithelial thickness variability (TVT) as objective dry eye markers. Significant improvement was observed in group A following cyclosporine A treatment, surpassing the improvements seen in the control group, across all metrics at the 12-month follow-up compared to the 1-month baseline. [33]

Similarly, Andre A. M. Torricelli et al. studied 642 eyes (524 LASIK and 118 PRK) and found that topical cyclosporine A was effective in optimizing patients for refractive surgery and managing new or worsened dry eye symptoms post-surgery.[34]

Jeewan Singh Titiyal et al.[35] and Lu Zhao et al.[36] conducted trials on patients undergoing femtosecond-assisted laser in situ keratomileusis (FS-LASIK) and Xiaofeng Zhu et al.[37] conducted a randomized trial with 151 patients undergoing SMILE (small incision lenticule extraction) found that topical 0.05% cyclosporine A was beneficial in maintaining ocular surface stability post-refractive surgeries.

In summary, the above studies have shown that topical cyclosporine not only alleviates ocular pain and dry eye symptoms and signs in post-refractive surgery DED patients with ocular pain but also effectively controls ocular inflammation.

Topical cyclosporine after cataract surgery

Yeon Woong Chung et al. conducted a study involving 32 newly diagnosed dry eye patients one week after cataract surgery. Each patient received twice-daily treatments of 0.05% cyclosporine in one eye and 0.9% normal saline in the other. Disease severity was assessed at 2 weeks, 1 month, 2 months, and 3 months using the Schirmer test I (ST-I), tear film break-up time (TBUT), corneal temperature measurements, and the Ocular Surface Disease Index

questionnaire. The eyes treated with 0.05% cyclosporine demonstrated significantly greater improvement compared to those treated with 0.9% normal saline.[38]

Similarly, Samer Hamada et al. [39], Min Seung Kang et al. [40] and Hanieh Ahmadi et al. [41] conducted separate clinical trials where participants' eyes were assigned to receive either topical 0.05% cyclosporine or artificial tears after routine cataract surgery and showed greater improvements in dry eye parameters with cyclosporine compared to artificial tears. Additionally, eyes receiving cyclosporine showed significantly better recovery of corneal sensation with significance at one month.

John A. Hovanesian et al. conducted an open-label, multicenter, prospective study involving seventy-five patients (75 eyes) who presented for cataract surgery with signs of dry eye disease. These patients were prescribed topical 0.09% cyclosporine twice daily for 28 days. Cataract surgery was performed 1 to 3 weeks after the second biometry visit. One month post-surgery, the absolute prediction error of spherical equivalent refractive outcome was 0.39 ± 0.30 D before treatment versus 0.33 ± 0.25 D after treatment ($P < 0.03$). The proportion of eyes achieving the target refraction was higher with measurements taken after cyclosporine treatment compared to pre-treatment measurements.[42]

In summary, dry eye symptoms can worsen after cataract surgery. The above studies have shown to be useful in treatment signs and symptoms of dry eye disease in patients post cataract surgery.

Topical cyclosporine after corneal transplantation

Raquel Esteves Marques et al. performed a meta-analysis to evaluate the efficacy and safety of adding topical cyclosporine A (CsA) to topical corticosteroids (CS) for preventing and treating corneal graft rejection following penetrating keratoplasty (PK). The combined regimen of CS and CsA was associated with higher rejection-free graft survival rates at 1 and 2 years. Subgroup analysis predominantly supported the use of 2% CsA for high-risk grafts.[43]

Samrat Chatterjee et al. conducted a prospective case series involving patients with fungal keratitis undergoing therapeutic penetrating keratoplasty (TPK). The study included 20 patients in the topical cyclosporine A (tCSA) group and 28 patients in the conventional treatment (CT) group, which received topical prednisolone acetate 1% drops. Postoperative treatment with topical 0.1% cyclosporine A appeared to improve graft survival, postoperative vision, and reduce the risk of primary infection recurrence in patients with fungal keratitis undergoing TPK. [44]

In summary, while topical cyclosporine has shown potential in preventing or reversing corneal graft rejection in some studies, further research is needed to confirm these findings.

Topical cyclosporine in ocular inflammatory diseases

Cyclosporine A in chronic follicular conjunctivitis

Anton M Kolomeyer et al. conducted a retrospective chart review spanning from 2001 to 2012, involving 12 patients (22 eyes) with chronic follicular conjunctivitis (CFC) treated with topical cyclosporine A (1%). They assessed several outcomes, including inflammation grade, visual acuity, concurrent corticosteroid therapy, effects on corticosteroid tapering, and any adverse effects. The study concluded that topical 1% cyclosporine A is an effective and well-tolerated treatment that reduces chronic inflammation and allows for the tapering of topical corticosteroids in CFC patients.[45]

Cyclosporine A in non-necrotizing stromal keratitis

Sanjay N Rao's study evaluated the efficacy of topical cyclosporine 0.05% (Restasis) in patients with herpes simplex virus non-necrotizing stromal keratitis who were unresponsive to topical prednisolone. Cyclosporine led to resolution of stromal keratitis in 10 out of 12 patients after one month, with a greater reduction in lesion area compared to prednisolone. However, four patients experienced a recurrence of stromal keratitis after discontinuing cyclosporine therapy.[46]

Cyclosporine A in allergic keratoconjunctivitis

Ozlem Eski Yücel et al. conducted a study with 30 patients suffering from vernal keratoconjunctivitis (VKC) who were resistant to topical corticosteroids, antihistamines, and mast cell stabilizers. The patients were treated with topical cyclosporine A 0.05% and evaluated at 4, 8, and 12 weeks. Topical cyclosporine A 0.05% was found to be an effective and safe alternative that reduced the need for corticosteroids in patients with resistant VKC.[47]

Annegret H Dahlmann-Noor et al. performed a single-group interventional study with 99 subjects to assess the impact of cyclosporine A (CsA) on managing atopic keratoconjunctivitis (AKC). They found that commercial preparations of CsA 1 mg/ml significantly reduced the need for additional topical corticosteroids and decreased the frequency of hospital clinic visits.[48]

Andrea Leonardi et al. evaluated the pooled outcomes of cyclosporine A cationic ophthalmic emulsion (CsA CE) in

pediatric and adolescent patients with VKC through the NOVATIVE (0.05%, 0.1%, or vehicle eye drops) and VEKTIS (0.1% QID or twice daily or vehicle) trials. They found that CsA CE significantly reduced corneal damage and was safe and well-tolerated in VKC patients.[49] Similar findings were reported by Elena Salami et al. who studied the effects of 0.1% cyclosporine in VKC patients.[50]

Cyclosporine A in pterygium

Ozlem Yalcin Tok et al. studied 31 patients with bilateral pterygium. Over a 1-year follow-up, the right eyes (treatment group) were treated with topical cyclosporine A, while the left eyes (control group) were not. Pterygium recurred in 4 (12.9%) of the treated right eyes compared to 14 (45.2%) of the control left eyes (p = 0.005). The control group had a 7.37 times higher risk of recurrence compared to the treatment group.[51]

Usha K Raina et al. (2024) investigated the safety and efficacy of topical cyclosporine A (CsA) and interferon alpha-2b, finding both to be effective new adjuvants with LCAT in preventing postoperative pterygium recurrence.[52]

SUMMARY

The numerous advantages of using CsA for treating ocular surface diseases, such as dry eye disease (DED), are well-recognized, positioning CsA formulations as a key component in the range of anti-inflammatory treatments available for managing DED. It may be used to treat ocular inflammation and allergic and immunological diseases of the eye at concentrations ranging from 0.05%- 2% as eye drops as shown in various studies. It is well-tolerated and effective for treating steroid-resistant and refractory ocular inflammatory conditions. This method is safe, highly effective, and non-invasive, making it suitable for long-term use in managing chronic anterior segment disorders and resistant conditions. It is also regarded as the preferred initial treatment for patients with ocular inflammation. Topical cyclosporine is being used in various forms like cyclosporine A cationic emulsion, water free cyclosporine, micellar nano-particulate (MNP) cyclosporine emulsion and cellulose acetate phthalate-based pH-responsive contact lens (CL) loaded with CsA. Many studies have proved topical cyclosporine useful in conditions like dry eye disease yet its uses in conditions like vernal keratoconjunctivitis and prevention of corneal graft reversal require further studies to ascertain its efficacy and safety more accurately.

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