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Cyclosporine as Postoperative Immunomodulating Agent in Penetrating Keratoplasty for Keratomycosis

Esteban Peralta MD[1*], Chris Kim MD[2], James Tian MD[1], Syed Ali Ahmed[3], Alan Carlson MD[1], Lloyd Williams MD[1]
[1]Duke University School of Medicine, Durham, NC
[2]University of Massachusetts Chan Medical School, Worcester, MA
[3]University of the Incarnate Word School of Osteopathic Medicine, Dr San Antonio, TX

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*Corresponding Author
Esteban Peralta MD
Duke University School of Medicine
2351 Erwin Rd, Durham, NC 27705
(919) 681-3937
E-mail: esteban@alumni.duke.edu

Introduction

Keratomycosis, or fungal keratitis, is an ocular infection that can lead to corneal blindness.[1,2] All antifungal agents for keratomycosis are fungistatic, and topical formulations exhibit poor corneal penetration.[2,3] As a result, medical therapy alone fails in 24-44% of cases.[1] In many cases, penetrating keratoplasty (PK) is an essential surgical intervention to eliminate infection and ultimately preserve ocular integrity. Topical corticosteroids are the standard for preventing allograft rejection, but they carry the risk of promoting fungal recurrence.[2,4,5] Topical corticosteroids are often delayed postoperatively, which increases the risk of early graft rejection.[1] An alternative immunomodulatory agent that mitigates inflammation without increasing susceptibility to fungal resurgence is therefore of significant clinical interest.

Topical cyclosporine A (tCSA), a peptide that inhibits calcineurin and prevents transcription of interleukin-2 and is a crucial mediator of T-cell activation and proliferation, has emerged as a potential therapeutic.[4,6,7,8,9] Beyond its immunosuppressive properties, cyclosporine has been shown to inhibit corneal neovascularization, an important factor in improving long-term graft survival.[10,11] Unlike corticosteroids, cyclosporine selectively modulates T-cell activity without impairing innate immune defenses such as phagocytic function.[4,6]

Commercially available tCSA formulations range from 0.05 to 0.10%, although specialty compounding pharmacies can produce higher concentrations.[6] In a prospective study, Perry and colleagues (2002) successfully used tCSA 0.5% with systemic antifungal therapy on 3 patients undergoing therapeutic PK for fungal keratitis.[4] Similarly, Chatterjee et al. (2022) found that tCSA 0.1% improved PK graft survival rates in keratomycosis while reducing recurrence risk in 20 eyes.[1] Another study showed that tCSA 2% in combination with topical corticosteroids enhanced rejection-free graft survival in pediatric PK cases.[12] In a randomized

controlled trial, tCSA significantly improved reversal of graft rejection when used alongside topical prednisolone.[13]

Building upon these findings, our study employed tCSA 2% as an immediate postoperative immunosuppressant which was then bridged to corticosteroids. We hypothesized that tCSA 2% would safely prevent allograft rejection and fungal recurrence following PK for keratomycosis.

Methods

A retrospective case series of patients with keratomycosis was conducted at the Duke Eye Center from 2023-2024. Six patients were identified who underwent therapeutic PK by a single, experienced corneal specialist after failure of medical antifungal therapy over an average of 2 weeks (range 0.5-3). Eyes were treated exclusively with tCSA 2% for at least 1 week before transitioning to prednisolone. Exclusion criteria included prior graft rejection or oral immunosuppressant use. Patients were then treated with tCSA 2% 6 times daily and transitioned to prednisolone after 1–2 weeks based on clinical assessment. Primary outcome measures included graft rejection or fungal recurrence. Additional measures included most recent visual acuity and graft clarity.

Results

Neither fungal recurrence nor graft rejection were observed, although 1 patient developed early suture-related inflammation related to poor adherence to the eyedrop regimen. Results are summarized in Table 1.

1. *Phaeohyphomycosis*: A patient working in water testing presented with a large corneal infiltrate, hypopyon, and an endothelial plaque. Preoperative treatment included oral and topical voriconazole and topical moxifloxacin for 3 weeks. Preoperative visual acuity was light perception (LP). Postoperative tCSA was administered for 14 weeks and tapered monthly. The addition of topical prednisolone was delayed 14 weeks due to history of steroid response. Visual acuity was 20/25 at postoperative month 12.

2. *Purpureocillium lilacinum*: A patient with primary open angle glaucoma status-post iStent (Glaukos) and Ex-Press shunt (Alcon) placement was initially diagnosed with blebitis and subsequent corneal ulcer complicated by endophthalmitis. Preoperative treatment included intravitreal vancomycin, ceftazidime, and voriconazole injections as well as a 3-week duration of topical voriconazole, natamycin, vancomycin, and tobramycin. Preoperative visual acuity was hand motion (HM). Postoperative tCSA was administered for 8 weeks. The addition of topical prednisolone was delayed by 4 weeks and overlapped for 4 weeks. Visual acuity was bare LP despite a clear graft at postoperative month 10.

3. *Purpureocillium lilacinum*: A contact lens wearer with ragweed exposure developed a central corneal ulcer. Preoperative treatment included topical voriconazole, natamycin, vancomycin, and tobramycin for 1 week. Preoperative visual acuity was HM. Postoperative tCSA was administered for 3 weeks. The addition of topical prednisolone was delayed by 2 weeks and overlapped by 1 week. Visual acuity improved to 20/40 at postoperative month 7.

4. *Aspergillus fumigatus*: A patient with prior PK for Fuchs' dystrophy developed a central epithelial defect, endothelial plaque, and hypopyon (Figure 1). Preoperative treatment included topical moxifloxacin, voriconazole, fortified vancomycin, and tobramycin for 3 weeks. Preoperative visual acuity was HM. Cultures revealed polymicrobial infection with drug-resistant *Serratia*, *Staphylococcus haemolyticus*, and *Aspergillus fumigatus*. Postoperative tCSA was administered for 8 weeks. The addition of topical prednisolone was delayed by 2 weeks and overlapped for 6 weeks. Visual acuity was 20/150 at postoperative month 6.

5. *Culvularia*: A patient developed a corneal infiltrate and plaque and hypopyon after hay exposure. Preoperative visual acuity was 20/60. Preoperative treatment included voriconazole, amphotericin, and ofloxacin for 2 weeks. Postoperative tCSA was administered for over 25 weeks with extended treatment course due to poor follow-up and compliance, leading to a suture-related infiltrate which resolved. The addition of topical prednisolone was delayed 1 week, overlapping for 24 weeks. Visual acuity was 20/70 at postoperative month 7.

6. *Scedosporium apiospermum*: A patient developed a central corneal ulcer with severe thinning. Preoperative treatment included oral voriconazole, topical voriconazole, and caspofungin for 3 days. Preoperative visual acuity was HM. Postoperative tCSA was administered for 16 weeks. The addition of topical prednisolone was delayed 2 weeks and overlapped for 14 weeks. The patient developed a large epithelial defect which resolved. Visual acuity was 20/25 at postoperative month 8 with scleral contact lens.

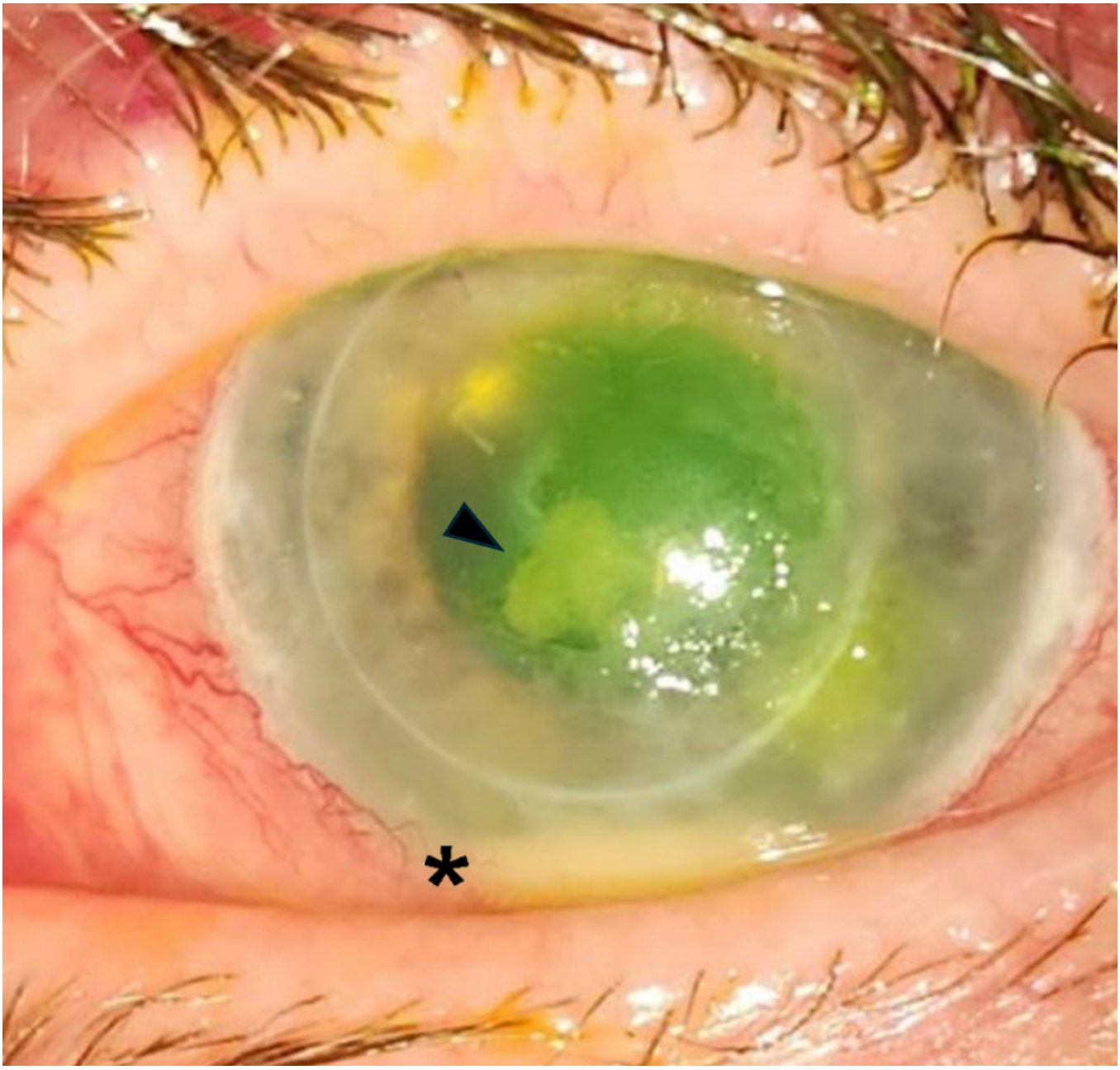

Figure 1. Central infiltrate (arrowhead) with hypopyon (asterisk) from polymicrobial infection including *Aspergillus fumigatus* in a patient with prior penetrating keratoplasty for Fuchs' endothelial dystrophy.

Discussion

This series highlights 6 cases of fungal keratitis treated with PK and tCSA 2% as primary immunosuppression. Despite wide variability in clinical presentation and pathogen, we demonstrate graft survival and absence of fungal recurrence with use of tCSA 2% in 6 cases.

One of the major challenges in managing fungal keratitis after therapeutic PK is balancing the need for immunosuppression to prevent graft rejection with the risk of promoting fungal recurrence. Despite the retrospective nature of this study, small sample size, and lack of control group treated with conventional corticosteroids, tCSA demonstrated favorable results compared to the typical clinical challenges of managing

such cases. Notably, graft rejection was not observed despite delayed steroid initiation. This aligns with previous studies by Perry and Chatterjee where tCSA improved graft survival in fungal keratitis.[1,4] The selective immunosuppressive action of cyclosporine, particularly its ability to modulate T-cell activity without impairing the host's antimicrobial defenses, likely contributed to this favorable outcome.

An important aspect of our protocol involved the transition from tCSA to topical prednisolone. Postoperative tCSA was used exclusively for approximately 2 weeks. Given the risk of graft rejection without steroid use, patients were transitioned to prednisolone approximately 2 weeks after exclusive tCSA use based on clinical judgment of graft status. In most cases, topical prednisolone dosed 4 times a day was introduced with a brief overlap period. This delay proved effective, although timing may vary depending on individual patient risk factors as demonstrated in the *Phaeohyphomycosis* case.

Final visual acuity reflected the severity of the underlying infection. While most patients experienced significant improvement, others had limited visual recovery, particularly those with extensive preoperative corneal involvement and other ocular comorbidities. Two patients recovered to 20/25 despite poor preoperative vision, while others, including cases with endophthalmitis or polymicrobial infections, had limited improvement. These challenges emphasize the need for close postoperative monitoring and a multidisciplinary approach.

Our findings suggest tCSA may be a useful agent in the post-transplant management of keratomycosis, allowing a buffer period for initiation of topical prednisolone. This case series contributes to the growing body of evidence supporting tCSA in corneal transplantation, particularly for fungal infections. Future studies should aim at further refining postoperative protocols to optimize visual outcomes and graft survival.

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Statement of Ethics

This case series adheres to patient confidentiality and ethical principles in accordance with the guidelines of the Declaration of Helsinki and relevant local regulations.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this topic.

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Table 1. Results summarized and labeled by fungal pathogen.

Fungal species	Preop VA	POM2 BCVA	tCSA duration (weeks)	tCSA frequency (doses per day)	prednisolone delay (weeks)	Overlap time (weeks)	Latest BCVA	Postop findings
Phaeohyphomycosis	LP	20/50	14	6-4-3-2-1 monthly	14	0	20/25 POM12	Iris incarceration
*Purpureocillium lilacinum**	HM at face	HM	8	6	4	4	Bare LP POM10	Peripheral haze
Purpureocillium lilacinum	HM	CF at 4 feet	3	6	2	1	20/40 POM7	N/A
*Aspergillus fumigatus***	HM	20/250	8	6	2	6	20/150 POM6	N/A
Culvularia	20/60	20/80	25+	6-4	1	24	20/70 POM7	Focal suture tract infiltrate, edema, mild ectasia
Scedosporium apiospermum	HM	20/150	16	6-5-4-3-2-1 q2week	2	14	20/25 POM8	Epithelial defect, iridocorneal adhesions

* The patient's clinical course was complicated by endophthalmitis prior to penetrating keratoplasty.
** Polymicrobial infection with drug-resistant *Serratia* and *Staphylococcus haemolyticus*
VA: Visual acuity
BCVA: Best-corrected visual acuity
POM: Postoperative month
LP: Light perception
HM: Hand motion
CF: Count fingers
tCSA: Topical cyclosporine
prednisolone: Prednisolone