Cornea 16(3): 284–288, 1997.

Topical Cyclosporin A in the Management of Postkeratoplasty Glaucoma

Henry D. Perry, M.D., Eric D. Donnenfeld, M.D.,
Anastasios J. Kanellopoulos, M.D., and Gayle A. Grossman, M.D.

Purpose. To evaluate the effect of substituting topical cyclosporin A 0.5% for topical corticosteroids in patients with postkeratoplasty glaucoma. **Methods.** Topical cyclosporin A 0.5% was prospectively substituted for topical corticosteroids to treat 25 patients with postkeratoplasty glaucoma. **Results.** Twenty-one (84%) of 25 patients showed a reduction in intraocular pressure (IOP) (range, 1–22 mm Hg; mean, 8.7 mm Hg). Follow-up ranged from 3 to 12 months (mean, 5.8). Graft clarity was maintained in all patients, with one allograft rejection episode. Thirteen patients were able to discontinue one or more glaucoma medication(s). **Conclusion.** Topical cyclosporin A 0.5% may be substituted for topical corticosteroids to aid in the management of postkeratoplasty patients with glaucoma. However, the resultant decrease in IOP may be associated with an increased risk for immune rejections.
Key Words: Cyclosporin A—Corticosteroids—Penetrating keratoplasty—Glaucoma.

Penetrating keratoplasty is the most successful and most frequently performed homologous transplant procedure in the United States with >43,000 corneal transplants performed annually (1). Glaucoma continues to be a serious clinical problem after penetrating keratoplasty because of frequency of occurrence, severity of disease, and difficulty in treatment (2–8). Unfortunately, glaucoma often leads to visual compromise. The use of topical corticosteroids in patients after keratoplasty can aggravate preexisting glaucoma and induce glaucoma in previously normal patients. Twenty to 30% of the general population respond moderately to steroids (9,10); 5–7% of the population respond with significant increases in intraocular pressure (IOP) >15 mm Hg (9–12) Corticosteroids produce a general ocular immunosuppression, potentiating the possibility of secondary infection, increasing the risk of secondary cataract formation, and often leading to delayed wound healing (13).

Cyclosporin A (Sandimmune; Sandoz Pharmaceuticals, East Hanover, NJ, U.S.A.), a highly specific immunomodulator that affects primarily T lymphocytes (14,15), does not inhibit the phagocytic system as greatly as do steroids, allowing the antimicrobial arm of the immune system to fight infection (14–17). Furthermore, cyclosporin A 0.5% does not inhibit wound healing, increase the IOP, or produce lens changes (14,15). Because the experience with cyclosporin A has been positive in the treatment of high-risk corneal transplants and immune graft rejections (15,18,19), we theorized that it may be beneficial in managing patients with glaucoma after keratoplasty.

Before initiating this study, we evaluated different concentrations and formulations of topical cyclosporine. We found the 0.5% suspension prepared from the commercially available 5% intravenous solution diluted with nine volumes of artificial tears to be the most well tolerated and efficacious. The purpose of this study, therefore, was to evaluate the effect of substituting topical cyclosporin A 0.5% for corticosteroids on a drop-for-drop basis in the management of patients with glaucoma after keratoplasty.

METHODS

Twenty-five patients seen in a corneal referral practice (H.D.P., E.D.D.) met the following criteria: (a) had undergone a penetrating keratoplasty be-

Submitted June 12, 1996. Revision received November 22, 1996. Accepted December 2, 1996.

From the Departments of Ophthalmology, North Shore University Hospital, Manhasset, and New York University Medical College (H.D.P., E.D.D., A.J.K., G.A.G.), and New York Eye and Ear Infirmary (H.D.P.), New York, New York; and Massachusetts Eye and Ear Infirmary (A.J.K.), Boston, Massachusetts, U.S.A.

Address correspondence and reprint requests to Dr. H.D. Perry, Lions Eye Bank for Long Island at North Shore University Hospital, 600 Northern Boulevard, Great Neck, NY 11021, U.S.A.

The authors have no proprietary interest in any aspect of this study.

TABLE 1. *Patient profile*

Sex	Age	Diagnosis	Preoperative glaucoma	Postoperative steroid	Months after keratoplasty
Male	57	Fuchs'	Yes	Fluorometholone	14
Male	47	Keratoconus	No	Prednisolone	28
Male	68	PBK	No	Prednisolone	7
Male	72	PBK	No	Fluorometholone	18
Female	85	PBK	Yes	Dexamethasone	4
Female	67	PBK	No	Dexamethasone	9
Male	69	PBK	No	Fluorometholone	30
Female	57	Fuchs'	Yes	Prednisolone	7
Female	62	Fuchs'	Yes	Dexamethasone	3
Male	22	Keratoconus	No	Dexamethasone	13
Male	73	PBK	No	Prednisolone	16
Female	86	Fuchs'	Yes	Fluorometholone	36
Male	68	Graft failure	Yes	Dexamethasone	6
Female	62	PBK	No	Dexamethasone	4
Female	80	ABK	Yes	Dexamethasone	5
Female	38	Keratoconus	No	Prednisolone	3
Male	71	PBK	No	Prednisolone	9
Male	62	PBK	No	Dexamethasone	5
Female	70	Climactic keratopathy	No	Dexamethasone	4
Male	74	PBK	No	Dexamethasone	6
Female	56	Fuchs'	Yes	Dexamethasone	14
Female	67	PBK	Yes	Dexamethasone	7
Male	34	Corneal scar	No	Prednisolone	14
Male	64	PBK	No	Dexamethasone	12
Male	57	PBK	No	Dexamethasone	8

PBK, pseudophakic bullous keratopathy; ABK, aphakic bullous keratopathy.

tween 3 months and 3 years ago; (b) on two successive readings, had an IOP of >22 mm Hg or difficulty tolerating current glaucoma medication(s); and (c) were taking topical corticosteroids (Table 1). All patients were advised of the potential adverse effects of topical cyclosporine treatment, including nephrotoxicity. Informed consent was obtained in all cases. A serum creatinine level was obtained in some patients before the start of the study.

The 0.5% topical concentration used in this study was prepared by diluting the intravenous cyclosporin A (Sandimmune; Sandoz Pharmaceuticals) 5.0% solution with nine volumes of artificial tears (Liquifilm Tears; Allergan Pharmaceuticals, Irvine, CA, U.S.A.). Patients were instructed to refrigerate the bottle of cyclosporin A 0.5% and to refill the prescription after 1 month. The substitution of cyclosporin A 0.5% for topical corticosteroids was done on a drop-for-drop basis. For example, if a patient was using dexamethasone 1% ophthalmic solution four times daily, this was discontinued, and topical cyclosporin A 0.5% was substituted four times daily. The IOP of these patients was initially monitored weekly or biweekly, and then monthly for a minimum of 3 months. An IOP determination was performed by an experienced technician by using a pneumotonometer in a masked fashion. The technician performed one determination per visit, and this was recorded in the patient's medical record. There was no allowance in these readings for diurnal variation. When the IOP decreased to <20 mm Hg and the patient was receiving glaucoma medications, one of the medications was discontinued. Five patients were arbitrarily chosen for cyclosporin A blood-level determinations.

RESULTS

Of the 25 patients enrolled in the study, 21 (84%) patients showed a reduction of IOP (Table 2). The reductions ranged from 1 to 22 mm Hg (mean, 8.7). Follow-up time ranged from 3 to 12 months (mean, 5.8). Graft clarity was maintained in all patients. One patient had an allograft rejection episode while using cyclosporin A 0.5% twice daily. The dose was increased to every hour for 1 week, every 2 h for 1 week, and four times daily. The allograft rejection episode was successfully resolved with graft clarity maintained. Seven patients discontinued at least one glaucoma medication, including five patients who discontinued oral carbonic anhydrase inhibitors [acetazolamide (Diamox) or methazolamide (Neptazane); Storz Ophthalmics, St. Louis, MO, U.S.A.]. Four patients discontinued topical echothiophate iodide (Phospholine Iodide; Wyeth-Ayerst Laboratories, Philadelphia, PA, U.S.A.), and four patients discontinued topical timolol maleate (Timoptic; Merck & Co., West Point, PA, U.S.A.). No patient had detectable levels of serum cyclosporine (all were <50 ng/

TABLE 2. *Summary of results*

mm Hg prior	Steroid dose	IOP meds	mm Hg after	Change in IOP	Months of follow-up	Glaucoma meds discontinued
23.5[a]	2	2	19	4.5	3	Acetazolamide
35[b]	4	2	20	15	12	Acetazolamide
29[b]	3	3	20	9	4	Phospholine iodide
31[a]	4	0	14	17	3	0
23[c]	2	1	19.5	3.5	3	0
44[c]	4	3	22	22	3	Methazolamide
15[a]	2	3	10	5	4	Acetazolamide
39[b]	4	1	25	14	3	Phospholine iodide
24[c]	2	2	16	8	4	Phospholine iodide
29[c,e]	12	1	15	14	6	β-blocker
28.5[b]	1	0	17.5	11	5	0
26[a]	1	1	19.5	6.5	4	0
23[c]	2	0	16	7	4	β-blocker
27[c]	2	0	20	7	5	0
28[c]	1	1	19	9	7	0
25[b]	4	1	22	3	3	0
27[d]	1	0	23	4	3	0
28.5[c]	2	0	24.5	4	4	0
26[c]	2	1	21	5	3	β-blocker
33[c]	4	1	11	22	8	β-blocker
27[c]	4	0	18	9	6	0
26[c]	4	3	19	7	4	Acetazolamide
30[b]	4	0	29	1	3	0
30[c]	1	2	19	11	3	Phospholine iodide
28[c]	4	1	27	1	3	0

IOP, intraocular pressure.
[a] FML.
[b] Pred Forte.
[c] Dexamethasone.
[d] Pred Mild.
[e] Rejection episode, resolved.

ml). No patient had an increased serum creatinine level.

DISCUSSION

The incidence of glaucoma associated with penetrating keratoplasty is high (2–8) not only because glaucoma was present before the penetrating keratoplasty or concurrent disease in the patient population considered for keratoplasty, but also because of the development of newly diagnosed glaucoma produced by the mechanisms of keratoplasty or postoperative management of the corneal graft (corticosteroid therapy) (6,7). Prolonged increased IOP occurs in 12–51% of eyes after penetrating keratoplasty (6,20–22) Two main variables are significantly predictive of postkeratoplasty glaucoma (2,5). The first is preexisting glaucoma; a 56–77% incidence of increased IOP after penetrating keratoplasty is attributed to preexisting glaucoma (5,6,8,22,23). The second condition is aphakia, with an incidence of 21–52%. The combination of penetrating keratoplasty with anterior segment revision, anterior vitrectomy, or intraocular lens removal also may be associated with increased postoperative IOP (5, 22,23).

The prolonged use of topical steroids is the mainstay of treatment after penetrating keratoplasty to decrease inflammation and prevent graft rejection. A chronic steroid-response glaucoma develops in patients sensitive to steroids (24). Discontinuation of the topical corticosteroid regimen may be difficult, depending on the corneal graft status. The need for corticosteroids in the glaucoma patient after keratoplasty routinely complicates the management of IOP control. We believe the mechanism for action of the observed pressure reduction in our study is the result entirely of the cessation of corticosteroids.

Management of postkeratoplasty glaucoma has been difficult. Medical management revolves around the well-known aqueous suppressants, usually β-blockers and carbonic anhydrase inhibitors. Miotics are less commonly prescribed because at least in part of shallowing of the anterior chamber, which may induce synechia formation. Miotics, most important, tend to induce intraocular inflammation by increasing the permeability of the blood aqueous barrier, which in turn potentiates graft rejection (25). When medical management is insufficient, argon laser trabeculoplasty is used (26). The degree of open angle and the ability to visualize the angle limit the use of argon

laser trabeculoplasty. If laser treatment is not effective or possible, the next step in management is trabeculectomy or glaucoma implant procedures or both and cyclodestructive procedures to control the IOP in grafted eyes (27–30). It is well known that surgical intervention in the patient after keratoplasty frequently leads to graft failure. We believe that topical cyclosporin A 0.5% may be safely substituted for corticosteroids in the management of these difficult patients with glaucoma after keratoplasty. In this problem group, the likelihood of steroid responsiveness approaches 92%. It is our experience that this substitution will routinely decrease IOP and may prevent surgical intervention.

Penetration of topical cyclosporine into the aqueous humor and serum has been shown to be low (15,31). In our patient group, serum determinations failed to reveal any significant serum levels of cyclosporine. Our primary concern in using topical cyclosporine is that with cessation of topical corticosteroids, there may be an increased incidence of immunologic graft rejection. Although one rejection episode occurred during the course of our study, this was managed by increasing the dose of topical cyclosporin A. All patients in this study, with the exception of the problem of glaucoma, had a relatively good prognosis for corneal transplantation. Only one patient could be considered high risk, having had graft failure resulting from an irreversible graft-rejection episode. This small pilot study cannot determine whether the substitution of cyclosporin A for corticosteroids increases the likelihood of graft-rejection episodes or is more dangerous to the patient. We await a double-masked controlled study to prove this point. However, in the patient after keratoplasty who is a steroid responder and has glaucoma, we believe that our results support substituting cyclosporine for corticosteroids.

The results of this pilot study suggest that substitution of topical corticosteroids with topical cyclosporin A 0.5% maintains satisfactory corneal graft clarity. Because a significant subpopulation of glaucoma patients after keratoplasty develops steroid-responding glaucoma, this substitution may help significantly in the prevention and management of ocular hypertension (24,32). Our experience consists of a nonrandomized trial of topical cyclosporin A 0.5%. Therefore the effect of topical cyclosporin A in all patients after penetrating keratoplasty has not been evaluated. We attempted to minimize bias by having all IOP measurements performed by a trained technician by using a pneumotonometer and blind to the status of the patient. For patients receiving glaucoma medications, their inclusion in the study may have increased their compliance, and therefore, included bias in the cyclosporin A effect. We found that the 0.5% dilution of cyclosporin A formulated from the intravenous solution had a lower discomfort level among our patients compared with higher concentrations (1–2%). None of the patients in the study discontinued cyclosporin A because of topical adverse effects, although several patients complained of mild to moderate irritation. Five patients had blood-level determinations for cyclosporin A that were all undetectable (<50 ng/ml). None of the patients developed increased serum creatinine levels during the study.

Topical cyclosporin A 0.5% in an artificial tear solution appears to be well tolerated and effectively promotes corneal graft clarity. In most patients with postkeratoplasty glaucoma who are receiving topical corticosteroids, a significant ocular hypotensive effect occurs that has not been attributed to cyclosporin A. The mechanism of action seems to be the removal of the agent causing secondary steroid-induced ocular hypertension or glaucoma. If routine patients with glaucoma are treated with corticosteroids, >90% will show an ocular hypertensive response to topical corticosteroids (33,34). In patients with glaucoma after keratoplasty, corticosteroids present a significant risk to the patient and routinely will add to the complexity of their postoperative management. The number of patients we studied was small and not randomized; therefore generalized conclusions cannot be drawn from these data. There is a strong suggestion that topical cyclosporin A may play an important role in the management of postkeratoplasty glaucoma, while promoting corneal graft clarity.

Acknowledgment: Supported in part by the Lions Club International Foundation, Oakbrook, IL.

REFERENCES

1. Eye Bank Association of America. *Eye Bank Association of America 1994 Statistical Report.* Washington, DC: EBAA, 1994:5.
2. Foulks GN. Glaucoma associated with penetrating keratoplasty. *Ophthalmology* 1987;97:871–4.
3. Thoft RA, Gordon JM, Dohlman CH. Glaucoma following keratoplasty. *Trans Am Acad Ophthalmol Otolaryngol* 1974;78:352–64.
4. Goldberg DB, Schanzlin DJ, Brown SI. Incidence of increased intraocular pressure after keratoplasty. *Am J Ophthalmol* 1981;92:372–7.
5. Karesh JW, Nirankari VS. Factors associated with glaucoma after penetrating keratoplasty. *Am J Ophthalmol* 1983; 96:160–4.
6. Polack FM. Glaucoma and keratoplasty. *Cornea* 1988;7:67–9.
7. Kirkness CM, Ficker LA. Risk factors for the development of post-keratoplasty glaucoma. *Cornea* 1992;11:427–32.
8. Simmons RB, Stern RA, Teekhasaenee C, et al. Elevated intraocular pressure following penetrating keratoplasty. *Trans Am Ophthalmol Soc* 1990;87:79–93.
9. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics: I. The effect of dexamethasone in the normal eye. *Arch Ophthalmol* 1963;70:482–91.

10. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics: II. The effects of dexamethasone in the glaucomatous eye. *Arch Ophthalmol* 1963;70:492–9.
11. Lewis JM, Priddy T, Judd J, et al. Intraocular pressure response to topical dexamethasone as a predictor for the development of primary open-angle glaucoma. *Am J Ophthalmol* 1988; 106:607–12.
12. Stewart RH, Kimbrough RL. Intraocular pressure response to topically administered fluorometholone. *Arch Ophthalmol* 1979;9:2139–40.
13. Leibowitz HM. Ocular toxicity of corticosteroids. In: Leopold IH, Burns RP, eds. *Symposium on ocular therapy, volume 2.* New York: Wiley, 1979;108–9.
14. Nussenblatt RB, Palestine AG. Cyclosporine: immunology, pharmacology, and therapeutic uses. *Surv Ophthalmol* 1986;31:159–69.
15. Belin MW, Bouchard CS, France S, et al. Topical cyclosporine in high-risk corneal transplants. *Ophthalmology* 1989; 96:1144–50.
16. Koponen M, Grieder A, Loor F. The effects of cyclosporins on the cell cycle of T-lymphoid cell lines. *Exp Cell Res* 1982;140:237–50.
17. Granelli-Piperno A, Keane M. Effects of cyclosporin A on T-lymphocytes and accessory cells from human blood. *Transplant Proc* 1988;20(suppl 2):87–91.
18. Zhao J-C, Jin X-V. Local therapy of corneal allograft rejection with cyclosporine. *Am J Ophthalmol* 1995;119:189–94.
19. Hoffmann F, Wiederholt M. Lokale behandlung des hornhaut-transplantates beim menschen mit cyclosporin A. *Klin Monatsbl Augenheilkd* 1985;87:92–6.
20. Beebe WE. Management of glaucoma in penetrating keratoplasty patients. *Refract Corneal Surg* 1991;7:67–9.
21. Gilvarry AE, Kirkness CM, Steele AD, et al. The management of post-keratoplasty glaucoma by trabeculectomy. *Eye* 1989;3:713–8.
22. Chien AM, Schmidt CM, Cohen EJ, et al. Glaucoma in the immediate postoperative period after penetrating keratoplasty. *Am J Ophthalmol* 1993;115:711–4.
23. Kenyon KR, Kenyon BM, Starck T, Hersh PS. Penetrating keratoplasty and anterior segment reconstruction for severe ocular trauma. *Ger J Ophthalmol* 1994;3:90–9.
24. Polack FM. Graft rejection and glaucoma. *Am J Ophthalmol* 1986;101:294–7.
25. Massry GG, Assil KK. Pilocarpine-associated allograft rejection in postkeratoplasty patients. *Cornea* 1995;14:202–5.
26. Van Meter WS, Allen RC, Waring GO, et al. Laser trabeculoplasty for glaucoma in aphakic and pseudophakic eyes after penetrating keratoplasty. *Arch Ophthalmol* 1988;106:185–8.
27. Binder PS, Abel RA, Kaufman HE. Cyclocryotherapy for glaucoma after penetrating keratoplasty. *Am J Ophthalmol* 1975;79:489–92.
28. Kirkness CM, Ling Y, Rice NSC. The use of silicone drainage tubing to control postkeratoplasty glaucoma. *Eye* 1988;2:583–90.
29. Beebe WE, Starita RJ, Fellman RL, et al. The use of Molteno implant and anterior chamber tube shunt to encircling band for the treatment of glaucoma in penetrating keratoplasty patients. *Ophthalmology* 1990;97:1414–22.
30. Klapper RM, Wandel T, Donnenfeld ED, Perry HD. Transscleral ND:YAG thermal cyclophotocoagulation in refractory glaucoma: Part I. A preliminary report. *Ophthalmology* 1988;95:719–22.
31. Mosteller MW, Gebhardt BM, Hamilton M, et al. Penetration of topical cyclosporine into the rabbit cornea, aqueous humor and serum. *Arch Ophthalmol* 1985;103:101–2.
32. Podos SM, Krupin T, Asseff C, Becker B. Topically administered corticosteroid preparations: comparison of intraocular pressure effects. *Arch Ophthalmol* 1971;86:251–4.
33. Armaly MF. Inheritance of dexamethasone hypertension and glaucoma. *Arch Ophthalmol* 1967;77:747–51.
34. Becker B. Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol* 1965;4:198–205.