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Long-term Outcome of Systemic Cyclosporine Treatment Following Penetrating Keratoplasty

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Purpose: To perform a retrospective study to evaluate the long-term outcome of systemic cyclosporine treatment as an adjunct to topical corticosteroid treatment after penetrating keratoplasty (PKP).

Methods: Twenty-six high-risk patients (27 eyes) who received systemic cyclosporine following PKP for an average of 5.4 months were compared with another series of 57 patients (57 eyes) who did not receive cyclosporine after PKP.

Results: Endothelial rejection developed in 2 cases during cyclosporine treatment and in 6 cases after discontinuation. The rate of rejection-free graft survival was similar between the treated and the control groups. The control group showed a significantly higher rate of graft survival than the treated group. As side effects in the treatment group, transient elevation in blood urea nitrogen or creatine developed in 7 cases. Increase in glutamete oxaloacetate transaminase (GOT) or glutamete pyrubate transaminase (GPT) developed in 4 cases. Severe side effects were absent throughout the series in both groups of patients.

Conclusion: Systemic cyclosporine treatment for several months did not reduce the incidence of rejection nor improve the rate of graft clarity in the long term in high-risk patients after PKP. **Jpn J Ophthalmol 2001;45:378–382** © 2001 Japanese Ophthalmological Society

Key Words: Cyclosporine, graft survival, penetrating keratoplasty, rejection, side effect.

Introduction

Owing to recent developments in surgical techniques and postoperative management, indications of penetrating keratoplasty (PKP) have been extended to high-risk patients with conditions of regrafting, bullous keratopathy, or chemical burn. One of the most important factors that affects the clinical outcome of PKP is allograft rejection. Because high-risk patients are more likely to experience allograft rejection than low-risk patients, their clinical outcome after PKP has not been good.[1] Although topical and systemic corticosteroids have been used traditionally to suppress the immune response, these are not effective for suppressing rejection. Cyclosporine A (CsA), a neutral, hydrophobic, cyclic endecapeptide metabolite of the fungus *Tolypocladium inflatum gans*, has a molecular weight of 1,202 Daltons, and prevents the uptake of interleukin-1 (IL-1) by T-inducer cells, thereby blocking the synthesis of IL-2.[2,3] Systemic CsA treatment has been used extensively to suppress rejection after renal, bone marrow, and liver transplantation.[3] However, as the development of renal or hepatic damage in patients after a normal dose of systemic CsA has been reported, systemic CsA treatment should be considered very carefully.[4,5] The suppressive effect of systemic CsA on allograft rejection after PKP has not been established.[6–8] We evaluated the long-term efficacy and the side effects of systemic CsA treatment after PKP in this report.

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Materials and Methods

We made a retrospective study of PKPs performed between June 1989 and January 1993 at the Tokyo University Hospital. Twenty-six patients (27 eyes) were treated after surgery with CsA in combination with corticosteroid eye drops (the CsA group). The 27 corneal transplants were performed on 17 male and 9 female patients. Informed consent was obtained from all patients. As the control, we made a retrospective study of 57 PKP cases during the same time period (the eyes of 29 male and 28 female patients) (the control group). These patients were treated postoperatively with topical corticosteroids but not with systemic CsA. In the CsA group, the preoperative diagnoses are shown in Table 1. The indications were mainly bullous keratopathy (55.5%), leucoma (14.8%), and herpetic keratitis (11.1%). In the control group, the indications were bullous keratopathy (20 cases, 35.1%), herpetic keratitis (14 cases, 24.5%), leucoma (11 cases, 19.3%), corneal dystrophy and degeneration (6 cases, 10.5%), alkali burn (3 cases, 5.3%), and keratoconus (3 cases, 5.3%). The number of PKP operations per case was 1.8 times (±1.2, SD) (first: 14 eyes, second: 9 eyes, third: 1 eye, fourth: 1 eye, fifth: 2 eyes) in the CsA group, and 1.2 times (±0.5, SD) (first: 49 eyes, second: 7 eyes, third: 1 eye) in the control group. The number of PKP operations per case was significantly more in the CsA group than in the control group ($P < .01$). The grade of preoperative corneal vascularization ($P = .70$) and anterior synechia ($P = .14$) were similar between these groups. In both these groups, subjects were randomly selected from patients who met at least one condition of the following four conditions; the first included corneal vascularization in one or more quadrants of the cornea preoperatively; the second included anterior synechia preoperatively; the third included diagnosed bullous keratopathy; the fourth included a history of graft failure. The mean period of CsA treatment was 5.4 months (±3.4, SD) (range, 3–13 months). The mean recipient age was 61.6 years (±13.7, SD) for the CsA group and 55.0 years (±18.5, SD) for the control group. The mean postoperative follow-up period was 54.9 months (±25.1, SD) for the CsA group (range, 10–92 months) and 61.8 months (±26.9, SD) for the control group (range, 5–103 months).

Donor eyes, enucleated aseptically, were maintained in preservation media (EP-II®, Kaken Pharmaceuticals, Osaka) at 4°C. Transplantations were done within 72 hours of enucleation. Lensectomy, anterior vitrectomy, or intraocular lens implantation was done simultaneously when necessary. The diameter of the corneal graft was 7.50–8.00 mm, and 0.25–0.50 mm larger than that of the recipient cornea. The grafts were sutured to the recipient corneas with interrupted 10-0 nylon sutures. Cyclosporine A was given to maintain a trough level of 100–150 ng/mL of whole blood. An initial dose of 5 mg/kg per day was given for 2 weeks after surgery, followed by 3 mg/kg per day thereafter. Both groups of patients received a subconjunctival injection of dexamethasone (1.2 mg) and ofloxacin ointment at the end of surgery. Systemic prednisolone (30–60 mg/day) and topical betamethasone (1 mg/mL), ofloxacin, and tropicamide were administered after surgery in both groups. Topical treatment was tapered off over several months; from six times a day postoperatively to four times a day at 3 months, three times a day at 6 months, and twice daily at 12 months. The corneal sutures usually were removed 12–18 months after surgery.

A corneal graft was defined as rejected when it became edematous and showed such signs of immunological rejection as a rejection line, keratic precipitates, or anterior segment inflammation. Patients who developed immunological rejection were treated intensively with topical and systemic corticosteroids. The usual treatment for allograft rejection included the instillation of betamethasone eye drops every 1 or 2 hours, and subconjunctival injection of 1.2 mg dexamethasone and systemic administration of prednisolone (30–60 mg/day).

Serum chemistry (glutamete oxaloacetate transaminase [GOT], glutamete pyrubate transaminase [GPT], blood urea nitrogen [BUN], creatine), blood picture, and urine examinations were performed every 1 or 2 months after surgery. When the levels of serum chemistry increased above the upper limit of normal, CsA was tapered. And when these levels increased 1.5 times above the upper limit of normal, CsA treatment was stopped. Blood pressure and incidence of myopathy were monitored.

Data are presented in graph and table forms. In graph form, graft survival and rejection-free graft survival curves were made by the Kaplan-Meier method,[9] and the results were analyzed by the log-rank test.

Results

Endothelial rejection occurred in 2 cases (cases 4 and 7) during CsA therapy and in 6 cases (cases 6, 12, 15, 22, 24, and 25) after discontinuation (Table 1). Sixty months after surgery, rejection-free survival

Table 1. Background and Outcome for Patients in This Study

Patient No.	Age	Sex	Diagnosis*	Number of Penetrating Keratoplasty	Anterior Synechia	Vascular Invasion†	Operation‡	Cyclosporine A Treatment (Months)	Follow-up (Months)	Outcome
1	64	Male	Stevens-Johnson Sydrome	1	−	3	PKP	6	38	Clear
2	65	Male	Leucoma	2	−	2	PKP	7	10	Endothelial disorder (10 months)
3	48	Male	Keratoconus	4	−	2	PKP	6	94	Endotheli disorder (6 months)
4	20	Female	CHED	2	−	0	PKP	12	82	Rejection (1 month)
5	63	Male	Aphakic bullous keratopathy	2	−	2	PKP	9	82	Clear
6	56	Male	Leucoma	5	+	2	PKP	13	92	Rejection (14 months)
7	53	Female	Bullous keratopathy (keratitis)	5	+	3	PKP	13	92	Rejection (8 months)
8	66	Male	Pseudophakic bullous keratopathy	2	−	2	PKP	9	73	Endothelial disorder (18 months)
9	52	Female	Aphakic bullous keratopathy	2	+	2	PKP	8	71	Endothelial disorder (32 months)
10	64	Male	Bullous keratopathy (Sato's ope)	2	−	1	PKP+ECCE +IOL	8	14	Clear
11	52	Male	Bullous keratopathy (Sato's ope)	2	−	2	PKP	6	68	Clear
12	63	Male	Aphakic bullous keratopathy	2	+	0	PKP+ Vitrectomy	3	30	Rejection (18 months)
13	78	Male	Aphakic bullous keratopathy	1	+	0	PKP	3	67	Clear
14	53	Male	Acid burn	1	+	3	PKP+KEP	3	65	Endothelial disorder (16 months)
15	78	Male	Bullous keratopathy (keratitis)	1	−	0	PKP+PI	3	62	Rejection (15 months)
16	71	Male	Aphakic bullous keratopathy	3	−	0	PKP+ Vitrectomy +PI	3	33	Endothelial disorder (28 months)
17	39	Female	Bullous keratopathy (POAG ope)	1	−	0	PKP+ECCE	3	64	Endothelial disorder (14 months)
18	76	Male	Aphakic bullous keratopathy	1	+	0	PKP	3	61	Endothelial disorder (7 months)
19	64	Male	Herpetic keratitis	1	+	3	PKP	3	48	Clear
20	71	Female	Lattice corneal dystrophy	2	−	0	PKP	3	20	Clear
21	75	Female	Aphakic bullous keratopathy	1	−	0	PKP+ Vitrectomy	3	58	Clear
22	66	Male	Leucoma	1	+	2	PKP+ECCE +IOL	3	16	Rejection (16 months)
23	76	Female	Aphakic bullous keratopathy	1	+	4	PKP+ Vitrectomy +IOL	3	18	Endothelial disorder (18 months)
24	45	Female	Bullous keratopathy (SACG)	1	+	0	PKP+ECCE	3	60	Rejection (18 months)
25	55	Male	Herpetic keratitis	1	−	3	PKP	3	61	Rejection (24 months)
26	70	Male	Leucoma	1	−	1	PKP	3	60	Clear
27	80	Female	Herpetic keratitis	1	+	0	PKP+Vitrectomy +ICCE	3	44	Endothelial disorder (19 months)

*CHED: congenital hereditary endothelial dystrophy, POAG: primary open-angle glaucoma, SACG: secondary angle-closure glaucoma.
†Vascular invasion: 0 = none, 1 = 1 quadrant, 2 = 2 quadrants, 3 = 3 quadrants, 4 = 4 quadrants.
‡PKP: penetrating keratoplasty, ECCE: extracapsular cataract extraction, IOL: intraocular lens implantation, KEP: keratoepithelioplasty, PI: peripheral iridectomy.

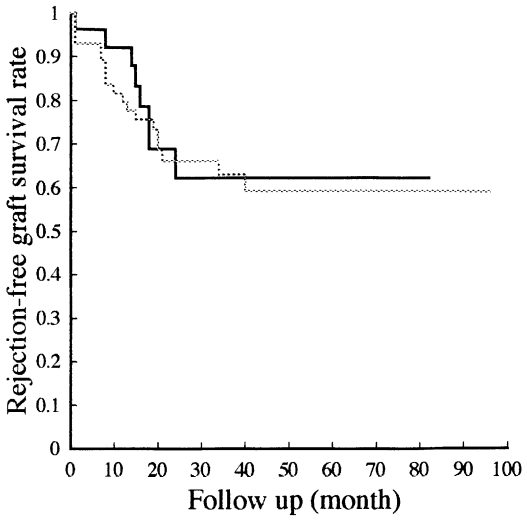

Figure 1. Rejection-free graft survival in cyclosporine A (solid line) and control (broken line) groups estimated by Kaplan-Meier method. Log-rank test: $P = .81$ (not significant).

rates (Figure 1) were similar for the CsA and control groups ($P = .81$). During CsA therapy (5.4 months), rejection-free survival rates (Figure 1)were similar for both groups ($P = .55$). Sixty months after surgery, graft survival rates (Figure 2) were statistically lower in the CsA than in the control group ($P < .05$). During CsA therapy (5.4 months), graft survival rates (Figure 2) were similar for both groups ($P = .78$).

During the period of systemic CsA treatment, the whole blood BUN or creatine levels temporarily were elevated over the normal limits in 7 patients, the whole blood GOT or GPT levels were elevated in 4 patients, and both the whole blood BUN or creatine and GOT or GPT levels, in 2 patients. The elevated values, however, reverted to normal levels when the dose of systemic CsA was tapered off or stopped. There was no patient whose CsA treatment was discontinued because of 1.5 times elevated values of the whole blood BUN, creatine, GOT, or GPT. Of 6 patients treated preoperatively for hypertension, 3 patients required additional hypertensive medication during CsA treatment. There was no patient who showed an abnormal blood picture or urine examination, or the presence of myopathy.

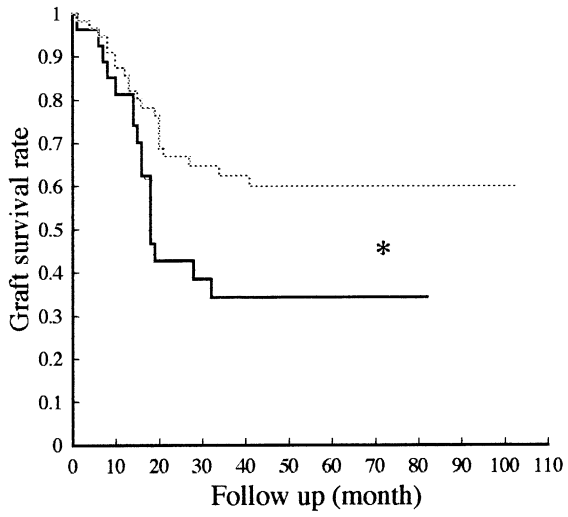

Figure 2. Graft survival in cyclosporine A (solid line) and control (broken line) groups estimated by Kaplan-Meier method. Log-rank test: $P = .02$ (*$P < .05$).

Discussion

In this study, we evaluated the long-term efficacy of systemic CsA treatment after PKP. Yamagami et al[8] reported the short-term efficacy of systemic CsA treatment after PKP. In our study, we evaluated many patients for longer observation periods. Yamagami et al[8] reported that the graft survival rates of the CsA group were 94% after 1 year and 84% after 2 years. In our study, the graft survival rates of the CsA group were 92% after 1 year and 62% after 2 years. The graft survival rates of the CsA group after 2 years were lower in our study than in Yamagami's report[8]; this was due to 5 cases (cases 12, 15, 22, 24, and 25), which showed rejection after Yamagami's examinations. Hill[6,10], Miller et al[11], and Reinhard et al[12] reported systemic CsA treatment for from 3 months to 1 year after PKP effectively reduced the risk of allograft rejection, and reported that CsA was effective in preserving allograft transparency in high-risk recipients. Maeda et al[7] reported that systemic CsA treatment for from 1 to 10 months after PKP had beneficial effects in 11 transplant patients. There were no cases of rejection during CsA treatment, but there were four cases of rejection and one opacity case after discontinuation. Their mean follow-up periods, however, were too short (21.6[6,10], 25[11], 24[12], and 13.8[7] months) to evaluate long-term efficacy. In our study, systemic CsA treatment after PKP was not effective in preserving allograft transparency in the CsA group. After discontinuation of CsA treatment, the rates of graft survival were lower in the CsA group than in the control group. It may be deduced that the number of PKP operations per case was significantly higher in the CsA group than in the control group ($P < .01$), or that our mean CsA treatment period (5.4 ± 3.4 months) was too short for calculating the rates of graft survival. In consideration

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of the adverse effects of systemic CsA treatment that have been reported, we have not used CsA for long-term treatment in this study.

Nephrotoxicity and hepatotoxicity are known complications of systemic CsA treatment. In our study, examinations of renal or hepatic functions such as GOT, GPT, BUN, and creatine were performed. There was transient increase of serum GOT or GPT in 4 patients, of serum BUN or creatine in 7 patients, and of both factors in 2 patients. This incidence was greater than in previous reports.[6,7] As the elevated values decreased to normal levels when the dose of systemic CsA was tapered off, it seems that systemic CsA treatment, if carefully monitored to detect these side effects, is relatively safe.

In our study, short-term systemic CsA treatment after PKP was not effective in reducing the long-term risk of allograft rejection in high-risk recipients. Moreover, there are many problems connected with systemic CsA treatment, such as side effects and the incidence of allograft rejection during therapy.[13] This is the time to reconsider the use of topical CsA treatment,[14–16] which has fewer adverse effects and can be used longer than systemic CsA.

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