

# Influence of Cyclosporin on Steroid-induced Cataracts After Renal Transplantation

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**Purpose:** To study the effect of cyclosporin (CsA) on steroid-induced cataracts in patients following renal transplantation.

**Methods:** The subjects comprise 140 patients who had undergone renal transplantation at Kanazawa Medical Hospital. These subjects had received ophthalmologic examinations prior to their surgery and subsequently over the span of 12 months following surgery. The charts of these patients were re-examined for this study. The subjects were divided into two groups: the conventional therapy group (Group C) that received azathioprine and methylprednisolone; and the triple therapy group (Group T) that received azathioprine, methylprednisolone, and CsA. There were 73 and 67 patients in Groups C and T, respectively. The cataracts were classified according to Crews' classification. Steroid-induced cataract was diagnosed when vacuoles were observed or opacity was evident in the posterior subcapsular region. Subjects who exhibited any lens opacity before renal transplantation were excluded from this study.

**Results:** The total amounts of systemic steroid administered during the first year and at the final observation period were significantly lower in Group T than in Group C. The prevalence of steroid-induced cataracts of grade 1 and above was 55% and 63% for the first year, 73% and 89% for the second year, 74% and 92% for the third year, and 83% and 96% for the fifth year in Groups C and T, respectively. By the third year, the percentage of subjects exhibiting corrected visual acuity <0.8 or receiving cataract surgery was significantly higher in Group T than in Group C. There was no significant difference in the total dose of steroids, in subjects with cataracts over grade 1 and those with grades 0 and 1, between these groups. In Group C, the total steroid pulse therapy dose was significantly higher in subjects with steroid-induced cataracts over grade 1 than in those with grades 0 and 1.

**Conclusions:** The observed rate of steroid-induced cataracts increased with the use of cyclosporin, despite a decrease in the total dose of systemic steroids. From this finding we suggest that the additional use of CSA may contribute to the development of steroid-induced cataracts. Steroid pulse therapy is considered a risk factor for the development of steroid-induced cataracts. **Jpn J Ophthalmol 2003;47:254–259** © 2003 Japanese Ophthalmological Society

**Key Words:** Cataract, corticosteroid, cyclosporin, prevalence, renal transplantation.

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## Introduction

Progress in renal transplantation technology has improved both the life expectancy and the quality of life of

patients suffering from chronic renal failure. However, as life expectancy improves, it has become increasingly important to consider the side effects of corticosteroids and accompanying immunosuppressive drugs employed in immunotherapy following renal transplantation. In order to reduce the side effects of the steroidal components, cyclosporin (CsA) is commonly administered in addition to two conventional primary immunosuppressive drugs, azathioprine and methylprednisolone.<sup>1,2</sup>

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Some side effects induced by postoperative steroid administration, including postoperative infection, gastrointestinal tract bleeding and femur head necrosis, have been reported as less prevalent with the additional use of CsA.<sup>1</sup> However, to the best of our knowledge, data regarding the influence of CsA treatment on steroid-induced cataracts has not been published. In this study we have examined the incidence and grades of steroid-induced cataracts in renal transplantation patients prior to and following the introduction of CsA.

### Materials and Methods

The charts of 140 patients who had undergone renal transplantation at Kanazawa Medical University Hospital between March 1975 and October 1995 were examined retrospectively. In all cases, the patients had frequently undergone examinations preoperatively, and postoperatively for more than 12 months on an outpatient basis at the Department of Ophthalmology of the Kanazawa Medical University Hospital. There were 95 men and 45 women, and the average age at the time of transplantation was  $29 \pm 8$  years (mean  $\pm$  SD) ranging between 9 and 48 years. The average postoperative follow-up period was  $73 \pm 50$  months (mean  $\pm$  SD), ranging between 12 and 235 months.

Based on the postoperative immunosuppression regimen, cases were divided into two groups; the conventional therapy group (Group C; surgery between March 1975 and December 1985), and the triple therapy group (Group T; surgery after 1986). The immunosuppressive drugs azathioprine and methylprednisolone were administered in combination to patients in Group C. An additional drug, CsA, was administered in combination with the other two drugs to patients in Group T. Group C consisted of 73 cases (49 men and 24 women) with an average age at transplantation of  $28.4 \pm 6.5$  years (mean  $\pm$  SD), and an average postoperative observation period of  $87 \pm 59$  months (mean  $\pm$  SD). Group T consisted of 67 cases (46 men and 21 women) with an average age at transplantation of  $30.1 \pm 8.9$  years

(mean  $\pm$  SD), and an average postoperative observation period of  $57 \pm 33$  months (mean  $\pm$  SD).

Mini-pulse therapy (methylprednisolone dose: 250–500 mg) was given on the day of transplantation to both groups, and the dosage was gradually reduced to a maintenance dose of 5 mg/day. Azathioprine (50–100 mg) was administered from the first post-transplantation day, and gradually reduced to a maintenance dose of 5 mg/day in both groups. The initial CsA dose was 8 mg/kg, and the maintenance dose was 2 mg/kg/day.

The cataracts were classified into four grades according to Crews' classification.<sup>3</sup> Steroid-induced cataracts were determined when lens opacity was exhibited or vacuoles were observed in the posterior subcapsular area. For analysis, we examined the relationship between the severity of the cataract and the steroid dosage. Classification of the cataract in cases that had undergone lensectomy was determined by the grade at the final observation before cataract surgery. Cases exhibiting lens opacity immediately prior to renal transplantation were excluded from the study. All the subjects were examined by slit-lamp biomicroscopy under maximum pupil dilatation. Subjects were examined pre- and postoperatively every 3 months for 12 months, and every 6 months thereafter.

The unpaired *t*-test was used to determine the statistical significance of the findings. A *P*-value of  $<.05$  was considered significant.

### Results

The amount of steroid that had been administered at 1 year after the renal transplant and at the final observation was significantly lower in Group T than in Group C (Table 1). The average length of time (mean  $\pm$  SD) before the onset of early changes of steroid-induced cataracts was  $14.1 \pm 15.6$  months, ranging between 2 and 105 months, and  $12.2 \pm 12.4$  months, ranging between 2 and 77 months after renal transplantation in Groups C and T, respectively. This difference was not statistically significant. The highest incidence of steroid-induced cataracts was between the 7th and 12th postoperative months in

**Table 1.** Total Amounts of Administered Steroid Following Renal Transplantation

	Average Age at Renal Transplantation (ys)	Period Following Transplantation (mo)	Administered Amounts of Steroid	
			1 Year After the Operation (mg)	At Final Observation (mg)
Group C (n = 73)	$28.4 \pm 6.5$	$87 \pm 59^*$	$10860 \pm 4373^*$	$37843 \pm 16832^*$
Group T (n = 67)	$30.1 \pm 8.9$	$57 \pm 33^*$	$8256 \pm 4661^*$	$22024 \pm 10475^*$

Values are mean  $\pm$  SD.

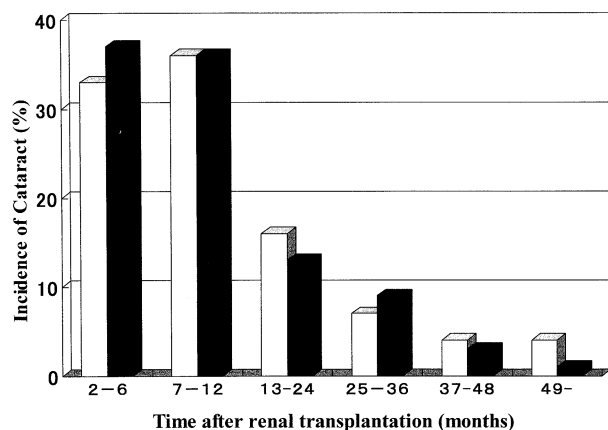
\**P* < .01.

Group C and between the 2nd and 6th postoperative months in Group T (Figure 1). This difference was significant ( $P < .05$ ).

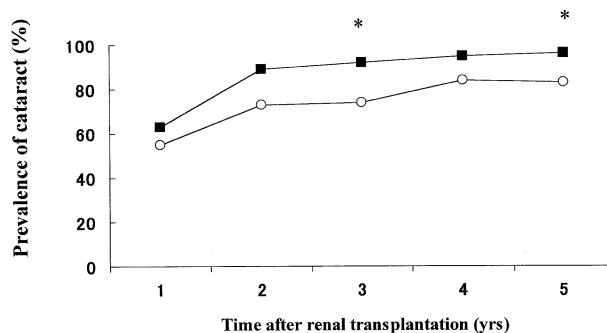
The differences in the prevalence of steroid-induced cataract, by grade, at different follow-up times for the two groups are shown in Figure 2. The prevalence of steroid cataracts of grade 1 and above was 55% and 63% for the first year, 73% and 89% for the second year, 74% and 92% for the third year, and 83% and 96% for the fifth year in Groups C and T, respectively. During the 5-year period following renal transplantation, the prevalence of cataracts was significantly higher in Group T than in Group C in the third and fifth years ( $P < .05$ ).

One year following renal transplantation, all cases in both groups exhibited steroid-induced cataracts classified as less than grade 2. The percentage of patients with transparent lenses was higher in Group C (46.4%) than in Group T (33.8%) (Figure 3A). This difference was not significant. At the final examination, cataracts of grade 2 or above were found in 54.2% of the subjects in Group C and 77.7% of those in Group T (Figure 3B). This difference was also not significant.

The patients with a corrected visual acuity of  $<0.8$  due to a cataract, and those who had undergone cataract surgery were considered to have progressive cataracts. At 3 years following renal transplantation and at the final examination, the cases in Group T exhibited a much higher prevalence of progressive cataracts than those in Group C (Figure 4). This difference was found to be



**Figure 1.** Distribution of the time of onset of steroid cataract in subjects who developed lens opacification after renal transplantation. The average length of time before the onset of early changes of steroid-induced cataract was 14.1 and 12.2 months after renal transplantation in Groups C and T, respectively. The period of the highest incidence of steroid-induced cataract ranged from the 7th to the 12th month in Group C and from the 2nd to the 6th month in Group T. □:Group C, ■: Group T.



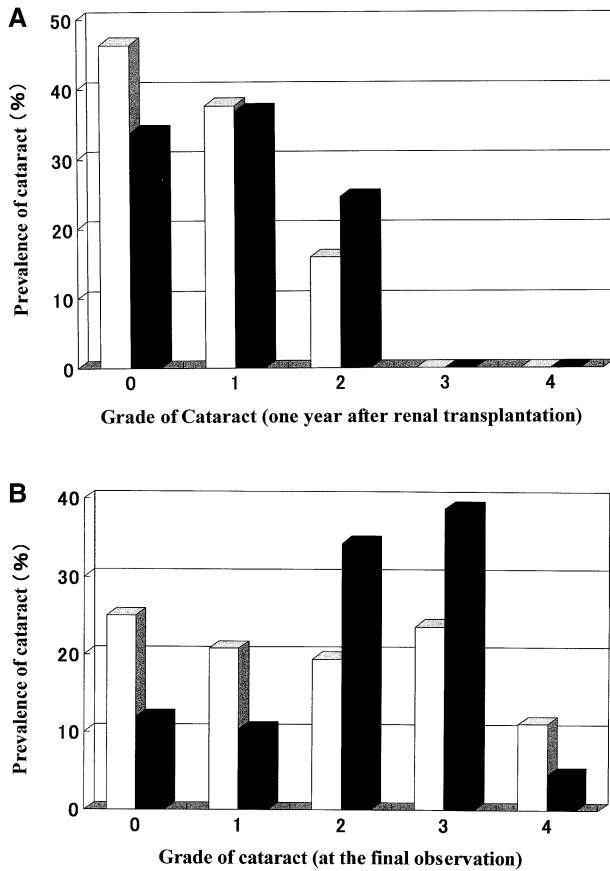
**Figure 2.** Prevalence of steroid-induced cataract during the 5 years following renal transplantation. Prevalence of steroid-induced cataract was markedly higher in Group T than in Group C at all times. ○: Group C, ■: Group T. \* $P < .05$ .

significant at 3 years following renal transplantation ( $P < .05$ ).

The cases were divided into two groups, depending on the cataract grade, to investigate any correlation between the steroid doses up to the final observation, and the development of cataracts (Table 2). The two groups comprised patients with incipient cataracts of grades 0-1 and patients with posterior capsular cataracts of grades 2-4, respectively. Although the relationship between the total dose of steroid and the degree of cataract was not significant in either group, the total amount of steroid administered in pulse therapy was significantly higher in the subjects with grades 2-4 than in those subjects with grades 0-1 in Group C ( $P < .01$ ). In Group T, the total amount of steroid administered in pulse therapy was also higher in the subjects with cataracts graded 2-4 than in those with cataracts graded 0-1; however, this difference was not significant. There was no significant difference in the average total amount of steroid administered in pulse therapy between Groups C (5,609 mg) and T (6,173 mg).

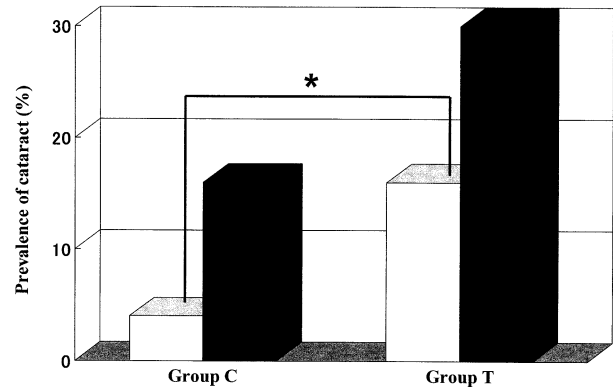
### Discussion

In spite of the numerous reports that the incidence of steroid-induced cataracts is correlated with the total amount of corticosteroids administered, no conclusive evidence has been presented to support these claims. Fournier et al<sup>4</sup> and Shun-Shin et al<sup>5</sup> reported that the correlation between these measures was not significant, whereas Adhikary et al<sup>6</sup> and Hilton et al<sup>7</sup> reported a significant correlation between the total amount of steroid and the incidence of cataract. In our study, we did not observe a significant correlation between the total amount of steroid administered and the prevalence of cataract at 1 year after renal transplantation in either



**Figure 3.** (A) Prevalence of steroid cataract 1 year after renal transplantation (grades 1–4). All cases in both groups had cataracts of grade 2 or less. Group C displayed more cases with transparent lenses. □: Group C, ■: Group T. (B) Prevalence of steroid cataract at the final examination (Grades 1–4). Group T displayed more cases of progressive cataract. □: Group C, ■: Group T.

group. Moreover, there was no significant difference between the total amount of steroid administered and the prevalence of cataracts leading to a corrected visual acuity <0.8, nor the prevalence of cataracts that had required cataract surgery in this series (unpublished data). Taniguchi et al,<sup>8</sup> of our research group, initially recorded that



**Figure 4.** Percentage of subjects with progressive cataracts. Three years following renal transplantation and at the final observation, Group T exhibited a much higher rate of progressive cataract cases than Group C. Progressive cataract: Cases with corrected visual acuity <0.8 due to cataracts and those that had undergone cataract surgery. □: 3 years after renal transplantation, ■: final observation. \**P* < .05.

subjects who had developed steroid-induced cataracts had been administered high doses of prednisolone (100 mg/day or more) for a significantly longer period than subjects with transparent lenses. Palvin et al<sup>9</sup> demonstrated that the incidence of cataracts was related to the frequency of graft rejection and, moreover, that the large amounts of steroid administered, because of graft rejection, were believed to have some bearing on the incidence of cataracts.

Our study showed clearly that, in Group C, the total amount of steroid administered in pulse therapy to patients that had developed cataracts of grade 2 and above was significantly higher than the amount administered to patients that had developed cataracts of grades 0–1. Whereas, in Group T with markedly higher total amounts of steroid in pulse therapy, no such significant difference was observed. The total dose of steroid administered at the final observation did not differ significantly between patients exhibiting cataracts of grades 0–1 and patients exhibiting cataracts of grades 2 and above.

**Table 2.** Total Amounts of Steroid and Pulse for Each Cataract Grade

Group	Cataract Grade	No. of Cases	Follow-up Period* (mo)	Total Amounts of Steroid at the Final Observation*	
				Total Amounts (mg)	Total Amounts of Pulse (mg)
Group C	0–1	34	85 ± 61	39193 ± 18942	4295 ± 3195 <sup>†</sup>
	2	39	89 ± 58	36701 ± 14976	6712 ± 4098 <sup>†</sup>
Group T	0–1	15	56 ± 32	23796 ± 12816	5833 ± 3923
	2	52	58 ± 34	21513 ± 9783	6272 ± 5891

\*Values are mean ± SD.

<sup>†</sup>*P* < .01.

From these results, we suggest that short-term administration of large amounts of steroid is a risk factor for cataract formation. Although steroid-induced cataract is typically accompanied by long-term steroid administration, as far as we know, no report exists for steroid-induced cataract following short-term steroid pulse therapy without a gradual decrease in optic neuritis.

Following steroid pulse therapy, long-term, low-level steroid maintenance therapy is generally employed in cases of renal transplantation. The combination of short-term administration of high levels of steroid followed by a long-term maintenance dosage is considered to markedly increase the incidence of steroid-induced cataract. Such a combination is frequently seen in uveitis patients, especially those with Vogt-Koyanagi-Harada disease. Among uveitis cases, the incidence of cataract is higher in those with Vogt-Koyanagi-Harada disease. Although it is not certain whether the cataracts seen in uveitis patients are due to either steroid or inflammation, reports have indicated that the incidence of cataract was almost 100% for chronic cases of Vogt-Koyanagi-Harada disease.<sup>10</sup> These cases usually receive high doses of steroid followed by a low dose of steroid and topical steroid treatment over a long period.

Although it has been reported that the total amount of steroid administered for immunosuppressive therapy following renal transplantation has decreased as a result of CsA usage,<sup>1</sup> the incidence of steroid cataracts in our study was higher in the subjects who received cyclosporin in comparison with those who had received conventional immunosuppressive therapy. No significant difference was observed between Groups C and T in terms of the total amounts of steroid dose administered or pulse therapy. The administered dose of azathioprine was also identical up to 1 year after the operation in the two groups. Thus, we believe that the combined use of CsA with the other two drugs is related to the increased incidence of cataracts. Moreover, the prevalence of cataracts of grade 2 and above was 54.2% in Group C and 77.7% in Group T even though the average postoperative observational period was shorter in Group T (57 months) than in Group C (87 months) at the final observation. We recognized the influence of CsA with respect to cataract incidence because Group T displayed a larger number of progressive cases. Unfortunately, there are no reports published regarding the incidence of cataracts attributable to the exclusive administration of CsA. It was because of this that we examined the relationship between CsA and steroid cataract. Although there is no experimental evidence, CsA appears to have an association with cataract as a syn-cataractogenic factor as reported by Hockwin and Wegener.<sup>11</sup> We believe that because our subjects were compromised hosts, this explanation might be viable.

Because CsA decreases the clearance of steroids,<sup>12</sup> CsA might influence the transitional amount of steroid in the lens. In addition, CsA is known to inhibit the action of P glycoprotein, a drug with excretory activity.<sup>13</sup> Typically, the inhibition of P glycoprotein appears to increase intracellular drug density. The interstitial density of the steroid also appeared to be a factor, which suggests the potential for elevated ocular steroid levels. Although we have not been able to verify this hypothesis directly, the influence of CsA in relation to steroid-induced cataract should be examined in future experiments. As the number of renal transplantation cases is increasing at our hospital, we plan to continue to clinically investigate this disease.

The results of this study have demonstrated that the combined use of CsA and steroids appears to increase the incidence of steroid-induced cataract following renal transplantation. Recently, cases of other types of organ transplantation surgery in addition to those for renal transplantation have been increasing in Japan. Consequently, the combined usage of CsA and steroid will be more frequent. Thus, it is necessary to examine the influence of combination therapy involving CsA not only on steroid-induced cataracts but also on other ocular side effects, such as steroid-induced glaucoma.

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