Pediatr Transplantation 2005: 9: 232–238. DOI: 10.1111/j.1399-3046.2005.00255.x
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Pediatric Transplantation

A prospective trial of steroid withdrawal after renal transplantation treated with cyclosporine and mizoribine in children: Results obtained between 1990 and 2003

Motoyama O, Hasegawa A, Ohara T, Satoh M, Shishido S, Honda M, Tsuzuki K, Kinukawa T, Hattori M, Ito K, Ogawa O, Yanagihara T, Saito K, Takahashi K, Ohshima S. A prospective trial of steroid withdrawal after renal transplantation treated with cyclosporine and mizoribine in children: Results obtained between 1990 and 2003. Pediatr Transplantation 2005: 9: 232–238. © 2005 Blackwell Munksgaard

Abstract: A prospective trial of adrenocorticostertoid (steroid) withdrawal after pediatric renal transplantation was begun in 1990. Ninety-four pediatric renal transplant recipients were enrolled in our multicenter study. Immunosuppressive therapy with cyclosporine (CyA), methylprednisolone (MPL), and mizoribine (MZ) was started after transplantation. MPL was reduced to administration on alternate days in 69 patients (73.4%) and was withdrawn in 27 patients (28.7%). Rejection episodes occurred in nine patients (33.3%) after withdrawal of MPL. It occurred within 3 months after withdrawal of MPL in two patients and more than 6 months in the others. Among them, two patients lost the grafts. Thirteen-year patient survival rate and graft survival rate were 94.6 and 83.1%, respectively. Forty-four of the 94 patients reached their final height. Mean final height was 155.0 cm in males and 146.3 cm in females and their height standard deviation score was −2.6 s.d., the same as that at the time of transplantation. Management of growth retardation before transplantation and further reduction in the steroid dose after transplantation will increase the final height of children with chronic renal failure.

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Key words: renal transplantation – steroid withdrawal – children – cyclosporine – mizoribine

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Accepted for publication 2 June 2004

There has been no solution to the problem of the growth disorder associated with adrenocorticosteroid (steroid) administration in children after renal transplantation. Irreversible impairment of physical growth is a major problem even in children in whom renal transplantation is successful. The efficacy of CyA in pediatric renal transplantation has been established. In addition, CyA has been shown to allow a reduction in the dose of steroids. Although trials of steroid withdrawal after renal transplantation have been reported, the timing of safe steroid withdrawal, the combined use of other immunosuppressive agents to reduce rejection and long-term

Abbreviations: AZA, azathioprine; CyA, cyclosporine; MZ, mizoribine; SDS, standard deviation scores.

prognosis after withdrawal are unclear (1). A multicenter prospective trial of steroid withdrawal after pediatric renal transplantation has been performed in Japan since 1990 (2). We attempted to reduce and then discontinue steroid administration by using an immunosuppressive protocol with CyA and MZ. MZ is a cytostatic or cytotoxic antibiotic, similar to AZA (3). Long-term results and physical growth of alternate-day steroid therapy followed by withdrawal in pediatric recipients treated with CyA and MZ have not been reported.

Patients and methods

Patients were all children before closure of the epiphysis, who underwent renal transplantation between 1989 and 2001. They were registered before renal transplantation and were treated with CyA, MPL, and MZ. CyA was started at the dose of 8–12 mg/kg, divided into two doses after transplantation. The whole blood trough level of CyA was determined by monoclonal antibody radioimmunoassay or fluorescent polarization immunoassay. The trough level of CyA for the first 2 months post-transplant was maintained at 200 ng/mL until 1995 and 300 ng/mL since 1996, and gradually reduced to 100 ng/mL, 3 months after transplantation. MPL was administered at the dose of 500 mg/m^2 intravenously during the operation and then as a single oral morning dose of 40 mg/m^2 postoperatively, which was reduced to 4 mg/m^2, 3 months after transplantation. MPL was withdrawn in patients without signs of rejection after the dose was decreased to alternate day 4 mg/m^2, when informed consent was obtained. MZ was started on the day before transplantation and continued at a dose of 100 mg/m^2 postoperatively. Anti-lymphocyte globulin (500 mg/m^2/day) was administered for 2 wk until 1995.

Diagnosis of rejection was made by taking into account clinical symptoms and changes in biochemical tests and urinalysis, using supportive evidence provided by radionuclide renogram, ultrasonography, and histopathologic findings of the biopsy specimen from the transplanted kidney. Creatinine clearance was calculated by the method of Schwartz et al. (4). Graft loss was defined as the need for dialysis or repeat transplantation. Patient and graft survival rates were calculated by the Kaplan–Meier method. The death of a patient was computed as graft loss although the graft was still functioning. The patient, in whom CyA was discontinued, was computed as a dropout.

Height SDS (5), target heights based on parental heights and percentages of weight for the height were calculated as follows:

Height SDS = (the patient's height − mean height for Japanese children)/(height s.d. for Japanese children).

Target height = mean parental height + 6.5 cm (in males), −6.5 cm (in females).

Percentage of weight = (weight of the patient − appropriate weight for the height of the patient) × 100/appropriate weight for the height of the patient.

Final height was defined as achieved when bone age had reached 16 yr for male patients and 14 yr for females, and their height did not increase over 1 yr. Bone age was evaluated using the Japanese version of the TW-2 method (RUS score) (6) by the same investigator, who was blinded to the clinical course of patients, and the ratio of bone age to chronological age (%) was calculated. Pubertal status was determined using Tanner's staging system (7). Patients with serum cholesterol level of 200 mg/mL or higher were regarded as having hypercholesterolemia. Statistical analysis was carried out using Student's *t*-test to compare mean values. A p-value of <0.05 was considered statistically significant. All p-values were two-sided.

Results

Patients

Ninety-four patients were enrolled in this study. Table 1 shows the profile of the patients. They received renal transplantation at a mean age of 9.5 yr. Sixty-eight children received continuous ambulatory peritoneal dialysis and 23 received hemodialysis before transplantation, while three received preemptive transplantation. Of the 90 living-related donors, 84 donors were parents with one haplo-identical HLA, 3 donors were parents with six HLA matches, 2 donors were grandmothers, and 1 donor was an aunt. Five patients received ABO-incompatible transplantation. As for primary renal diseases, chronic glomerulonephritis included IgA nephropathy in six patients, membranoproliferative glomerulonephritis in one patient, and crescentic glomerulonephritis in one patient. Histological diagnosis of six patients with nephrotic syndrome was not obtained. Of three patients with chronic pyelonephritis, one patient had reflux nephropathy and urinary tract malformation in two patients was not obtained.

Table 1. Profile of patients

Number of patients (male/female)	94 (53/41)
CAPD/HD/preemptive	68/23/3
Age at transplantion (yr)	9.5 ± 4.4 (1.3–17.6)
Living-related/cadaver donor	90/4
Primary/second grafts	90/4
Follow-up post-transplantation (yr)	7.7 ± 3.6 (0.1–13.7)
Primary renal disease	
Dysplasia/hypoplasia	32
Focal segmental glomerulosclerosis	16
Chronic glomerulonephritis	10
Nephrotic syndrome	6
Alport's syndrome	4
Polycystic kidney disease	3
Drash syndrome	3
Juvenile nephronophthisis	3
Posterior urethral valves	3
Chronic pyelonephritis	3
Wilm's tumor	3
Congenital nephrotic syndrome	2
Cystinosis	1
Renal vein thrombosis	1
Cortical necrosis	1
Unknown	3

CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis; preemptive, preemptive transplantation.

Results of transplantation

After renal transplantation, patients were followed-up for 7.7 yr on average. Four patients died. One patient with functioning graft died of malignant lymphoma and three patients died after their grafts were lost. Twelve patients lost the graft. Causes of graft loss were acute rejection in four patients, chronic rejection in four, recurrence of renal diseases in three (focal segmental glomerulosclerosis in one, crescentic glomerulonephritis in one, and IgA nephropathy in one) and primary non-function in one. The four acute rejection episodes occurred in three patients treated with daily MPL and one patient withdrawn from MPL. The four chronic rejection episodes occurred in two patients treated with daily MPL, one with alternate-day MPL and one withdrawn from MPL. Thirteen-year patient survival rate was 94.6% and graft survival rate was 83.1%. The clinical course of renal transplant recipients is shown in Fig. 1. MPL was reduced to alternate-day dosing in 69 patients (73.4%). Fifteen of the 69 patients treated with alternate-day MPL returned to daily administration of MPL, because of chronic rejection in four patients, acute rejection in two, relapse of focal segmental glomerulosclerosis in one, non-compliance for medication in one, and seven patients reached their final height. Among the 69 patients treated with alternate-day MPL, MPL was withdrawn in 27 patients (28.7%) at 3.6 ± 1.9 (0.8–8.3) yr after transplant and at the age of 11.5 ± 3.8 (2.6–19.8) yr on average. Eleven (40.7%) of the 27 patients with MPL withdrawn resumed MPL, because of rejection in nine patients, the onset of malignant lymphoma in one and parents' anxiety over rejection in one. Finally, 16 patients with functioning grafts continued MPL withdrawal for 3.2 ± 1.9 (0–7.7) yr. Creatinine clearance of the 16 patients was 36.8 mL/min/1.73 m^2 in one patient and 50 mL/min/1.73 m^2 or higher in the others at the last observation. As of the last examination, 37 patients were receiving MPL daily and 29 were receiving MPL on alternate days. Concerning graft function, creatinine clearance was 50 mL/min/1.73 m^2 or higher in 68 patients, between 25 and 50 mL/min/1.73 m^2 in 13 patients, and 25 mL/min/1.73 m^2 or less in one patient. In the 24 patients with acute or chronic rejection, CyA was switched to tacrolimus 3.2 ± 3.3 (0.1–11.8) yr after transplant. In 13 patients who received ABO-incompatible or ABO-minor-mismatched transplantation, AZA was used instead of MZ from the time of transplantation. In six of these patients, AZA was replaced with MZ over 3 months after transplantation. Moreover, MZ was switched to AZA in 10 patients. In six patients, MZ was switched after the onset of rejection, in three patients after relapse of primary renal diseases and in one after onset of malignant lymphoma. In eight patients, MZ was switched to mycophenolate mofetil after the onset of rejection. MZ was not reduced because of hepatic dysfunction or leukopenia.

Rejection

The first episode of acute rejection was observed within 1 month in 35 (37.2%) of 94 patients, within 3 months in 39 (41.5%), and within 6 months in 41 (43.6%). The histopathologic grade of seven acute rejection episodes was obtained and determined to be grade I in one, grade II in four, and grade III in two episodes according to the Banff classification (8). Treatment consisted of a high dose of MPL administration by bolus injection in all patients, anti-lymphocyte globulin or deoxyspergualin in 17 patients and OKT 3 monoclonal antibody in seven patients. Rejection episodes were noted in 11 patients after the initiation of alternate-day treatment. Two episodes occurred within 3 months and nine episodes 4.2 ± 3.1 (0.9–7.8) yr after the start of alternate-day MPL. One of the 11 patients developed graft loss. Two of 10 rejection episodes in nine patients occurred within 3 months and the others 2.8 ± 2.0 (0.5–4.2) yr after MPL withdrawal. Two of the nine patients developed graft loss.

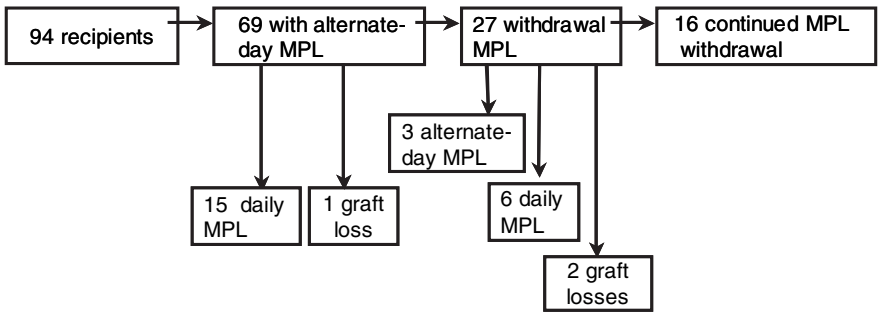

Fig. 1. Clinical course of renal transplant recipients and the current status of methylprednisolone (MPL) administration.

Physical growth

The height SDS at the time of transplantation was −2.6 ± 1.6 s.d. Alternate-day treatment or withdrawal of MPL was continued for 0.3 yr or more and physical growth was evaluated in 61 patients (72 times) and 23 patients (23 times). Alternate-day treatment of MPL was started at the age of 11.2 ± 3.8 (4.9–22.3) yr and continued for 3.9 ± 3.1 (0.3–10.5) yr. Withdrawal of MPL was started at the age of 12.0 ± 3.6 (4.4–17.7) yr and continued for 3.3 ± 1.7 (0.5–7.7) yr. The height SDS increased significantly after withdrawal of MPL, compared with that at the time of transplantation ($p = 0.002$) and before withdrawal of MPL ($p = 0.001$) (Table 2). The ratio of bone age to chronological age in 61 patients increased significantly from 83.8 ± 14.7 to 88.4 ± 13.3% during alternate-day therapy ($p = 0.007$). However, the ratio of bone age to chronological age in 18 patients withdrawn from MPL was 95.2 ± 14.5% before withdrawal of MPL and 93.2 ± 12.3% after withdrawal of MPL. In the 40 patients (23 males, 17 females), we evaluated for serial bone ages, including 28 patients treated with alternate-day administration of MPL and 12 patients withdrawn from MPL, whose serum creatinine level was 1.1 ± 0.4 mg/dL and creatinine clearance was 84.2 ± 27.7 mL/min/1.73 m^2 at the last evaluation, their growth curves according to chronological age and bone age are shown (Fig. 2). The 40 patients received transplantation before 12 yr of bone age. At the time of transplantation, their chronological age was 8.8 ± 3.6 yr and bone age was 7.3 ± 3.0 yr. Height s.d. was −1.6 ± 0.9 s.d. in nine patients, −2.1 ± 1.6 s.d. in 16 patients and −3.3 ± 1.5 s.d. in 19 patients at the chronological age of 5, 10, and 14 yr and −0.8 ± 0.8 s.d. in 16 patients, −1.1 ± 1.3 s.d. in 28 patients and −1.8 ± 1.0 s.d. in 19 patients at the bone age of 5, 10, and 14 yr. Female patients started menstruation at the chronological age of 12.8 ± 1.3 yr and bone age of 11.7 ± 1.1 yr, and their Tanner stage was 2. Tanner stage 2 was noted in males of 12.2 yr of age and females of 11.6 yr of age based on chronological age and defined as the start of puberty (Table 3). Growth gradually reduced to −2 s.d. during puberty. Forty-four patients (21 males, 23 females), including 30 patients treated with alternate-day MPL and 12 patients withdrawn from MPL during the course, reached the final height. They received transplantation at the age of 12.1 ± 3.1 (6.0–17.0) yr in males and 11.0 ± 3.4 (5.2–17.6) yr in females and reached final

Table 2. Changes in height standard deviation score during alternate-day administration and withdrawal of MPL

At transplantation (n = 93)	Alternate-day administration of MPL (n = 72)		Withdrawal of MPL (n = 23)	
	Before	After	Before	After
−2.6 ± 1.6	−2.4 ± 1.6	−2.3 ± 1.7	−2.0 ± 1.6	−1.5 ± 1.5
		NS		p = 0.001
	p = 0.002			

MPL, methylprednisolone.

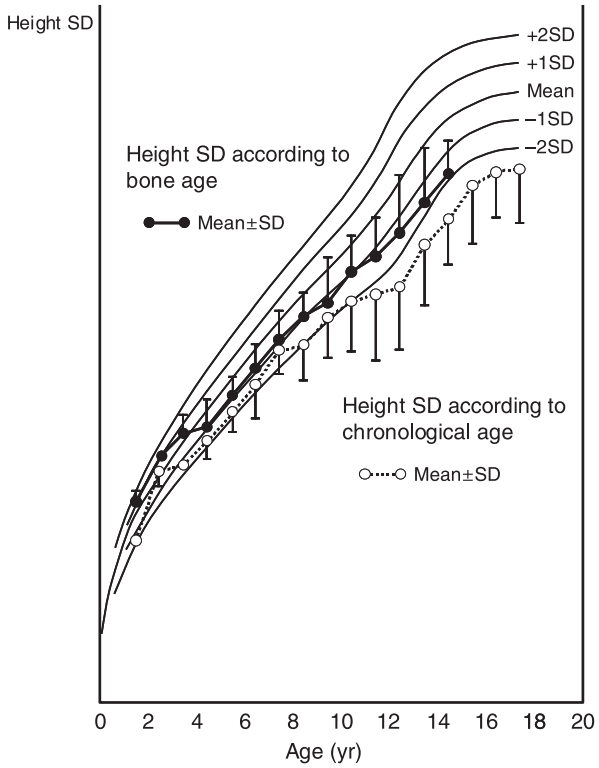

Fig. 2. Growth curves in 40 patients treated on alternate day or after withdrawal of methylprednisolone who had good graft function and were evaluated for serial bone ages.

Table 3. Relation among Tanner stage, chronological age, bone age, and height

Tanner stage	2 (n = 23)	3 (n = 21)	4 (n = 23)	5 (n = 15)
Chronological age (yr)				
Male	12.2 ± 1.4	13.6 ± 2.1	17.6 ± 3.8	21.2 ± 3.4
Female	11.6 ± 2.3	14.0 ± 2.4	15.4 ± 3.0	18.9 ± 3.0
Bone age (yr)				
Male	11.3 ± 0.7	13.0 ± 1.0	14.3 ± 1.6	16.1 ± 0.1
Female	9.9 ± 1.5	10.4 ± 1.2	12.9 ± 1.5	14.7 ± 0
Height (cm)				
Male	135.9 ± 7.4	143.9 ± 10.6	153.6 ± 9.0	157.3 ± 6.8
Female	127.7 ± 11.8	138.4 ± 14.6	145.9 ± 12.1	148.7 ± 10.3

height at the age of 20.1 ± 2.7 (17.0–26.9) yr in males and 18.7 ± 3.1 (14.2–24.9) yr in females. Height SDS of the 44 patients was −2.6 ± 1.7 (−8.3–0.2) s.d. at the time of transplantation and −2.6 ± 1.9 (−6.8–0.4) s.d. at the final height. The mean final height was 155.0 ± 10.7 (131.7–170.1) cm in males and 146.3 ± 9.6 (129.0–160.2) cm in females, compared with the mean Japanese adult height of 170.8 cm in males and 158.1 cm in females. Parental heights of 38 patients (18 males, 20 females) were obtained. The final height was 10.3 ± 8.9 (4.0–30.9) cm below the target height on average.

The percentage of weight was 102.8 ± 15.3% before alternate-day administration of MPL and 101.6 ± 18.2% after alternate-day administration of MPL in 66 patients. It was 101.9 ± 14.4% before withdrawal of MPL and 101.8 ± 16.6% after withdrawal of MPL in 23 patients. There were no significant differences.

Hypertension

Fifty-two patients (55.3%) received antihypertensive drugs 1 wk after transplantation, but the number of patients receiving antihypertensive drugs decreased to 31 (32.9%), 27 (28.7%), 18 (19.1%) and 21 (22.3%), 1 month, 3 months, 6 months, and 1 yr after transplantation. There were no difference among daily administration of MPL, alternate-day administration of MPL, and withdrawal of MPL.

Hypercholesterolemia

Hypercholesterolemia was noted in 81 patients (86.2%) throughout the observation period. Serum cholesterol level of 205 ± 40 mg/dL before alternate-day treatment of MPL decreased to 186 ± 36 mg/dL after alternate-day treatment of MPL ($p = 0.01$) in 56 attempts. Serum cholesterol level was 181 ± 37 mg/dL before 19 attempts at MPL withdrawal and 183 ± 36 mg/dL after withdrawal.

Adverse reactions and other complications

Infectious diseases attributed to immunosuppressive therapy included 10 patients with cytomegalovirus infection, which developed into pneumonia in two patients, and four patients with herpes zoster. Cytomegalovirus infection occurred 4–10 wk after transplantation and herpes zoster infection 2 wk to 5 months after transplantation. Nine of the 10 cases of cytomegalovirus infection and three of the four cases of herpes zoster infection occurred after treatment for acute rejection. Two patients with acute nephrotoxicity because of CyA were observed. Malignant lymphoma was noted in two patients. One of the patients died. Chemotherapy was completed and the graft is functioning in another patient. There was no aseptic necrosis of femoral capital epiphyses, glucose intolerance or leukoencephalopathy. Cataracts after transplantation were noted in 17 of the 81 patients (21.0%) who were examined for cataracts. They occurred 3.0 ± 2.6 (0.3–7.2) yr after transplantation.

Discussion

Recent data from the North American Renal Transplant Cooperative Study on pediatric renal transplantation showed that a 5-yr graft survival rate was 80% for living donors and 65% for cadaver donors (9). We attempted to reduce and then discontinue steroid administration by using CyA and MZ and obtained favorable patient and graft survival rates. Previous reports of steroid withdrawal after pediatric renal transplantation are listed in Table 4 (10 – 18). In our results, the percentage of successful MPL withdrawal was low, compared with other reports, because a second transplantation from a cadaver donor cannot be expected in Japan for cultural and

Table 4. Reports of steroid withdrawal after pediatric renal transplanatation

Reference	Immunosuppressive therapy	Time since transplant (months)	Withdrawn patients (%)	Restart of steroid (%)	Graft loss after withdrawal (%)	Follow-up (yr)
Tejani et al. (10)	CyA	4–5	52	24	0	0.8
Hodson et al. (11)	CyA	0	100	50	30	3.1
Reisman et al. (12)	CyA	14	81	46	8	3.5
Klare et al. (13)	CyA, AZA	2–6	73	38	17	5.2
Ghio et al. (14)	CyA	6	83	29	0	3.1
Ingulli et al. (15)	CyA	Over 6	45	58	9	4.9
Chao et al. (16)	CyA, AZA	Over 6	64	72	8	2.3
Chakrabarti et al. (17)	FK	6	90	24	12	4.9
Sarwal et al. (18)	FK, MMF, daclizumab	0	100	11	0	1.7

CyA, cyclosporine; FK, tacrolimus; AZA, azathioprine; MMF, mycophenolate mofetil.

religious reasons, and we were not able to obtain informed consent for steroid withdrawal. According to the report on renal transplantation by the Japan Society for Transplantation, renal transplantation in 95 Japanese patients < 19 yr of age performed in 2002 was from 85 living donors and from 10 cadaver donors (19).

Growth failure in children after renal transplantation is multifactorial. The main contributing factors are steroid treatment and reduced graft function. The growth inhibitory effects of steroids probably involve an alteration in the secretory pattern of growth hormone, inhibition of insulin-like growth factor-1 bioactivity, alteration in insulin-like growth factor-1 binding protein, and direct effect on the skeletal tissue matrix. The growth rates in children with well-functioning grafts, who are receiving relatively low doses of steroids, generally increase during the first 2 yr after transplantation and subsequently decline (20). In regard to age of transplantation, a young recipient with bone age delay will show catch-up growth throughout mid-childhood. Bone age advances in parallel with the chronological age during this period. However, growth velocity declines at the time of the expected onset of puberty, even in patients with good graft function, with a further delay in bone age (21). The onset and further milestones of puberty are delayed by an average of 2 yr and the pubertal height gain is reduced to about 50% of normal in children after transplantation (22). Rees et al. (23) reported that growth velocity declined at the expected age of the normal pubertal growth spurt with a delay in the appearance of secondary sexual characteristics in children who received alternate-day steroids after transplantation. Hokken-Koelega et al. (24) reported final height in 52 patients who received steroids daily or on alternate days as well as AZA. Median difference between final height and target height was 15.0 cm for males and 15.4 cm for females. Aschendorff et al. (25) also reported that the target height for nine patients treated with CyA and low-dose prednisolone could not be achieved. The difference between final height and target height was 4 cm for males and 7 cm for females. Offner et al. (26) revealed similar results of growth after transplantation with CyA. When children, whose height SDS was -1.5 ± 1.5 s.d. at the time of transplant, were treated with AZA and a high-dose prednisolone regimen, their final height was -2.2 ± 1.5 s.d. In their results of patients treated with CyA and low-dose prednisolone, height SDS was -1.6 ± 1.4 s.d. at the time of transplantation and -1.6 ± 1.7 s.d. at the final height. In our results, physical growth improved during MPL withdrawal. However, the mean height SDS decreased gradually and the final height fell short of our expectations, which was similar to previous reports. In our evaluation of longitudinal growth curve, pubertal development and final height, steroid effects could not be excluded because of a small number of patients who had MPL withdrawal. Incidence of hypertension was relatively low in our patients and serum cholesterol levels decreased after reduction of MPL.

The results of this study confirmed the safety of alternate-day MPL therapy followed by withdrawal. It appears that a slow MPL taper begun late in the transplant course is the safest protocol (1, 2). Steroid reduction improved physical growth and final height, compared with reported growth in patients treated with AZA and high-dose steroids after transplantation. In Japanese children maintained on dialysis treatment, a mean annual loss of -0.26 s.d. in height was seen. Management of growth retardation before transplantation and further reduction in steroids after transplantation will improve the final height of children with chronic renal failure.

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