

Final height in a prospective trial of late steroid withdrawal after pediatric renal transplantation treated with cyclosporine and mizoribine

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Abstract: A prospective trial of corticosteroid (steroid) withdrawal after pediatric renal transplantation was started in 1990. Fifty-eight recipients with functioning grafts reached their final height. They were transplanted at a mean age of 10.7 yr. Immunosuppressive therapy with CyA, MP, and MZ was started after transplantation. MP was reduced to an alternate-day dose in 49 patients and was withdrawn in 23. Their mean height SDS was -2.4 at the time of transplantation and -2.1 at their final height. Mean final height was 157.9 cm in men and 147.6 cm in women. In 18 patients who had been withdrawn from MP for more than two yr before reaching final height, mean age at transplantation was 8.9 yr. Their mean height SDS of -2.2 at the time of transplantation increased to -1.6 at their final height ($p = 0.02$), and mean final height was 163.8 cm in men and 147.8 cm in women. The height SDS in all 58 patients was maintained during the immunosuppressive therapy with steroid minimization, and final height SDS increased in recipients older than five yr at transplantation with steroid withdrawal.

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Growth depression is a well-known side effect of corticosteroid (steroid) therapy, and despite successful transplantation, impaired linear growth remains a major clinical problem in children after renal transplantation (1, 2). CyA has allowed us a reduction in the dose of steroids. A multicenter

prospective trial of steroid withdrawal after pediatric renal transplantation has been performed in Japan since 1990. We attempted to reduce and also discontinue steroid administration using CyA and MZ. We reported the acute rejection episodes and increased height SDS during steroid withdrawal in 1997 (3). Growth according to chronological age, bone age, and pubertal status in these patients was reported in 2005 (4). To our knowledge, adult height after steroid withdrawal in patients undergoing renal transplant has not been reported (1).

Abbreviations: CyA, cyclosporine; MP, methylprednisolone; MZ, mizoribine; NAPRTCS, North American Renal Transplant Cooperative Study on pediatric renal transplantation; rhGH, recombinant human growth hormone; SDS, standard deviation score.

Patients and methods

Ninety-four children received renal transplantation before closure of their epiphyses between 1989 and 2001. Profiles of 94 patients are shown in (4). They were treated with CyA, MP, and MZ, as described in the previous report. MP was reduced to 4 mg/m² three months after transplantation. MP was withdrawn in patients without rejection after the dose was decreased to alternate-day dose of 4 mg/m², when informed consent was obtained. One patient died, 11 lost their grafts, 24 were still growing at the end of the study, and 58 patients with functioning graft reached their final height. rhGH was used in one patient with growth hormone deficiency (4).

Creatinine clearance was calculated by the method of Schwartz et al. (5). Height SDS (6) and target heights based on parental heights were calculated as follows:

$$\text{Height SDS} = \frac{(\text{the patient's height} - \text{mean height for Japanese children})}{(\text{height s.d. for Japanese children})}$$

$$\text{Target height} = \text{mean parental height} + 6.5 \text{ cm (in men), } -6.5 \text{ cm (in women).}$$

Final height was defined as achieved when bone age had reached 16 yr for male patients and 14 yr for women and their height did not increase over one yr. Bone age was calculated using the Japanese version of the TW-2 method (RUS score) (7). The results are expressed as mean \pm standard deviation and range. Statistical analysis was carried out using Student's *t*-test to compare mean values (Excel 2002; Microsoft, Tokyo, Japan). To determine the influence on gain of height after transplantation, multiple regression analysis (JMP 8.0, 2009; SAS Institute, Cary, NC, USA) was carried out. Parameters of age at transplantation, height at transplantation, and withdrawal from MP were used. *p* Value of <0.05 was considered statistically significant.

Results

Fifty-eight patients (30 men and 28 women) reached their final height. They received transplantation at the mean chronological age of 10.7 yr (bone age of 9.6 yr). Final height was reached at 18.7 ± 1.5 (15.4–22.2) yr in men and 17.3 ± 1.9 (14.2–23.3) yr in women. At the time of final height, creatinine clearance (mL/min/1.73 m²) was 75.7 ± 28.0 (23.3–141.2) and was <25 in one patient, between 25 and 50 in eight patients and more than 50 in 49. They were followed up to 25.4 ± 4.8 (14.2–35.1) yr of age. Of the 58 patients, 49 were treated with alternate-day MP, and 23 were withdrawn from MP. In the 23 patients withdrawn from MP, it was reduced to alternate-day administration 1.3 ± 1.1 (0.5–5.2) yr after transplantation and was continued for 3.1 ± 2.4 (0.2–7.5) yr. MP was withdrawn 4.3 ± 2.9 (0.8–13.8) yr after transplantation and was discontinued for 3.7 ± 1.8 (0.5–8.1) yr. At

the time of withdrawal from MP, the patients' ages were 13.4 ± 4.0 (8.3–26.0) yr, height SDS was -2.5 ± 1.9 (-6.6 to 1.4), and creatinine clearance was 109.8 ± 33.0 (65.7–174.6) mL/min/1.73 m². MP was resumed in five patients, because of chronic rejection in four and the onset of malignant lymphoma in one (8). Of 35 patients who were not withdrawn from MP, seven patients (four boys of 8.0, 12.3, 12.6, and 14.6 yr of age and three girls of 5.5, 10.9, and 14.3 yr of age at transplantation) continued MP because they had reached final height. MP was continued because of relapse of focal segmental glomerulosclerosis in two patients, suspicion of non-compliance in 1, and rejection episodes or anxiety over rejection in the others.

The mean height SDS of the 58 patients when they reached the final height (-2.1) was slightly better than that at the time of transplantation (-2.4), but the difference was not significant (*p* = 0.08). The mean final height was 157.9 cm in men and 147.6 cm in women, compared with the mean Japanese adult height of 170.8 cm in men and 158.1 cm in women (Table 1). Parental heights of 50 patients (27 men and 23 women) were obtained. The final height was 9.2 ± 8.1 cm below the target height, and the range of the final height was between 30.9 cm below to 6.5 cm above the target height.

Mean final height SDS in five recipients aged 1–5 yr, 40 recipients aged 6–12 yr, and 13 recipients older than 13 yr at the time of transplantation was -0.7, -2.5, and -1.3, respectively, and there was no significant difference (Table 2). There was also no difference in final height and graft function among the following three groups: nine patients with daily MP administration, 26 with alternate-day MP administration, and 23 withdrawn from MP (Table 3). Age at transplantation in patients withdrawn from MP was lower than in the other two groups, and no

Table 1. Profiles of pediatric renal transplant recipients who reached final height

Number of patients (men/women)	58 (30/28)
Age at transplantation (yr)	
Chronological age	10.7 ± 3.4 (2.3 to 17.6)
Bone age	9.6 ± 3.2 (1.8 to 15.3)
Height SDS	
At transplantation	-2.4 ± 1.6 (-8.3 to 1.6)
At final height	-2.1 ± 1.7 (-5.9 to 0.6)
Final height (cm)	
Men	157.9 ± 9.4 (136.6 to 174.4)
Women	147.6 ± 9.4 (128.4 to 160.2)

SDS, standard deviation score.

Table 2. Steroid administration and height SDS in recipients aged 1–5 yr, 6–12 yr, and older than 13 yr at transplantation

	1–5 yr	6–12 yr	>12 yr
Number of patients	5	40	13
Steroid administration			
Daily	0	2	7
Alternate days	3	17	6
Withdrawal	2	21	0
Height SDS			
At transplantation	-1.7 ± 0.9	-2.6 ± 1.6	-2.0 ± 1.5
At final height	-0.7 ± 0.8	-2.5 ± 1.8	-1.3 ± 0.9

SDS, standard deviation score.

Table 3. Height SDS, graft function, and age at transplantation in nine patients with daily steroid administration, 26 with alternate-day steroid administration, and 23 withdrawn from steroid

	Daily	Alternate-day	Withdrawal
Number of patients	9	26	23
Height SDS			
At transplantation	-2.1 ± 1.3	-2.5 ± 1.7	-2.3 ± 1.4
At withdrawal	–	–	-2.5 ± 1.9
At final height	-2.0 ± 1.5	-2.3 ± 1.8	-1.9 ± 1.6
Ccr (mL/min/1.73 m ²)	67.4 ± 25.6	75.6 ± 25.5	79.1 ± 31.8
Age at transplantation (yr)			
Chronological age*	14.2 ± 1.9	11.0 ± 3.6	9.1 ± 2.4
Bone age*	12.4 ± 2.3	9.4 ± 3.3	8.7 ± 3.0

SDS, standard deviation score; Ccr, creatinine clearance at final height.

*Chronological and bone ages of the three groups were significantly different.

patient older than 13 yr at the time of transplantation was withdrawn from MP (Tables 2 and 3). There was no significant association between height gain after transplantation, age at transplantation, height at transplantation, and withdrawal from MP on using multiple regression analysis.

Of the 23 patients withdrawn from MP, the period of withdrawal from MP was short in three patients (0.5 yr in one patient and 1.1 yr in one because of chronic rejection and 1.9 yr in one because of malignant lymphoma), and MP was withdrawn after final height in two patients. In the remaining 18 patients (seven men and 11 women) who had been withdrawn from MP for more than two yr before they reached their final height, their mean height SDS increased from -2.2 at the time of transplantation to -1.6 at the time when they reached their final height ($p = 0.02$). They received renal transplantation at the mean chronological age of 8.9 yr (bone age of 8.4 yr). MP was reduced to alternate-day administration 1.4 ± 1.2 (0.5–5.2) yr after transplantation and was continued for 2.7 ± 2.3 (0.2–7.5) yr. MP was withdrawn 3.8 ± 2.0 (0.8–8.3) yr after transplantation and was discontinued for

Table 4. Profiles of patients who had been withdrawn from steroid for more than two yr before their final height was reached

Number of patients (men/women)	18 (7/11)
Age at transplantation (yr)	
Chronological age	8.9 ± 2.4 (5.2 to 12.9)
Bone age	8.4 ± 3.1 (3.7 to 13.5)
Height SDS	
At transplantation	-2.2 ± 1.1 (-4.4 to -1.0)
At withdrawal	-2.4 ± 1.6 (-6.6 to 0)
At final height	-1.6 ± 1.4 (-5.6 to 0.6)*
Final height (cm)	
Men	163.8 ± 8.5 (150.2 to 174.4)
Women	147.8 ± 7.6 (128.4 to 157.0)

SDS, standard deviation score.

* $p = 0.02$ when compared to height SDS at transplantation.

4.0 ± 1.7 (2.0–8.1) yr. At the time of withdrawal from MP, their age was 12.7 ± 2.5 (8.3–17.7) yr, height SDS was -2.4 ± 1.6 (-6.6 to 0), and creatinine clearance was 114.6 ± 35.5 (65.7–174.6) mL/min/1.73 m². During the period of MP withdrawal, they grew 16.9 ± 13.4 (1.0–47.4) cm and gained height SDS of 0.6 ± 0.9 (-1.8 to 2.3). Their creatinine clearance was 90.3 ± 35.1 (33.1–164.2) mL/min/1.73 m² when they reached their final height. The mean final height was 163.8 cm in men and 147.8 cm in women (Table 4). Multiple regression analysis revealed a significant negative association between gain of height after transplantation and age at transplantation ($R^2 = 0.899$, estimate of -4.16, $p = 0.006$). There was no significant association between height at transplantation and height gain after transplantation. Parental heights of 15 patients (seven men and eight women) were obtained. The final height was 6.4 ± 4.7 (-11.5 to 1.8) cm below the target height.

Discussion

Growth failure in children after renal transplantation is caused by multiple factors. The main contributing factors are steroid treatment and reduced graft function. The growth inhibitory effects probably involve an alteration in the secretory pattern of the growth hormone, inhibition of insulin-like growth factor-1 bioactivity, and alteration in insulin-like growth factor-1 binding protein. Those children who have well-functioning grafts and receive relatively low doses of steroids during the first two yr after transplantation grow, but the growth rates subsequently decline. The age of transplantation is also important. The NAPRTCS reported that only infants and preschool age children (2–5 yr) exhibited catch-up growth post-transplantation

Table 5. Height SDS at transplantation and final height in reports of pediatric renal transplantation

Reference	Period of transplant	No. of patients	CyA	Steroid	rhGH	Mean height-SDS	
						At transplant	At final height
Potter et al. (13)	1964–1983	29	–	Daily	–	–1.8	–2.3
Offner et al. (14)	1970–1982	35	–	Daily	–	–1.5	–2.2
Steenvoorde et al. (15)	1973–1985	24	–	Daily or ADT	–	–1.8	–2.1
Offner et al. (14)	1982–1993	49	+	Daily	–	–1.6	–1.6
Fine et al. (11)	1987–1996	273	+	NA	–	–2.2	–2.3
Englund et al. (12)	1981–1994	24	+	ADT	6 cases	–1.7	–1.1
Janssen et al. (16)	1988–1996	17	+	Daily or ADT	17 cases	–2.7	–1.9

CyA, cyclosporine; rhGH, recombinant human growth hormone; SDS, standard deviation score; ADT, alternate-day; NA, not available.

(9). A young recipient with delayed bone age usually shows catch-up growth throughout mid-childhood. However, growth velocity in patients with good graft function on alternate-day steroids seems to decline during puberty (10), as shown in our result (4). Reduced creatinine clearance ($< 40\text{--}50\text{ mL/min/1.73 m}^2$) has a significant negative effect on final height (11, 12).

Height SDS at transplantation and at final height in reports of pediatric renal transplantation is shown in Table 5 (11–16). Patients treated with azathioprine and steroid showed deterioration in final height SDS, while height SDS was maintained after transplantation in children treated with CyA and low-dose steroid. Increased final height SDS is reported in recipients treated with rhGH after transplantation. Adult height in 25–60% of children after renal transplantation was below -2 of mean adult height SDS despite various clinical interventions such as steroid minimization and rhGH therapy (2, 15, 17).

In our previous results, growth improved during MP withdrawal (3, 4). In this study, the height SDS increased during the immunosuppressive therapy with steroid minimization, and final height SDS increased even in recipients older than five yr of chronological age at transplantation in whom steroid was withdrawn. MP withdrawal for more than two yr before reaching final height was associated with increased final height. Japanese children normally reach their adult bone maturity at bone age of 16 yr in men and 14 yr in women (7). Therefore, MP withdrawal before 14 yr of bone age in boys and 12 yr of bone age in girls is important to increase the final height. There was no significant increase in final height SDS shown in preschool age recipients in this report. According to multiple regression analysis, younger recipients had better height gain after transplantation. The number of recipients aged 1–5 yr at the time of transplantation was too small to draw conclusions, and no one in the group was withdrawn from MP for

more than two yr before reaching their final height. In recipients older than 13 yr at transplantation, MP should be withdrawn early after transplantation before reaching final height. Randomized trial of early (on post-transplant day 5) steroid withdrawal after pediatric renal transplantation showed six months' outcome without an increased risk of rejection or graft loss (18).

We attempted to minimize steroid administration and withdrawal using CyA and MZ. Final height improved, compared with the reported growth in patients treated with azathioprine and high-dose steroids. However, final height was still below the target height and mean Japanese adult height. More aggressive management of growth retardation before transplantation may improve the final height of children with chronic renal failure. NAPRTCS showed that the mean height SDS at transplantation was -2.2 in 1987 and improved to -1.5 in 1999 and to -1.3 in 2007 (9). After this present study group, height SDS in 84 children transplanted between 2002 and 2008 and registered in the next prospective trial was -1.9 at transplantation. The strategy of starting rhGH therapy at a younger age during the course of chronic renal failure and the administration of rhGH after renal transplantation in severely growth-retarded children, in addition to steroid withdrawal, may improve their final height (2, 4, 19, 20).

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