Growth after Renal Transplantation in Prepubertal Children: Impact of Various Treatment Modalities

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ABSTRACT. A retrospective study evaluated posttransplant growth of 70 prepubertal children during the first 2 y after renal transplantation (RTx). Immunosuppressive treatment consisted of prednisone administered either daily or on alternate days in combination with either azathioprine or cyclosporin A. The increment in height standard deviation score for chronologic age during the first 2 y after RTx was less than 0.5 SD for 70% of the study population. The predictive factors for posttransplant growth were determined by evaluating several factors and treatment modalities singly and simultaneously in a multiple regression analysis. Patients with the most severe growth retardation at RTx appeared to have the most pronounced growth spurt after RTx, but even they never had complete catch-up growth, and 2 y after RTx they were still shorter than those with less severe growth retardation at RTx. Alternate-day instead of daily prednisone administration had a significantly positive influence, whereas a high cumulative dose of prednisone, azathioprine instead of cyclosporin A therapy, and a persistently reduced GFR (GFR < 50 mL/min/1.73 m²) had a significantly negative influence on catch-up growth during the 2 y after RTx. Other factors, such as gender, chronologic and bone age at RTx, primary renal disease, duration of initial dialysis, repeat RTx, and target height SD score for chronologic age, whether evaluated singly or simultaneously with other significant factors, appeared to have no significant influence on post-RTx growth. Thus, 70% of the prepubertal children do not experience appreciable catch-up growth during the first 2 y after RTx. Optimization of pretransplant height appears very important. Immunosuppressive treatment with cyclosporin therapy in combination with a minimal dose of alternate-day prednisone would then result in optimal posttransplant growth, particularly if the GFR remains above 50 mL/min/1.73 m². (*Pediatr Res* 35: 367–371, 1994)

Abbreviations

RTx, renal transplantation
hSDS_CA, height standard deviation score for chronologic age
CsA, cyclosporin A
Aza, azathioprine

SDS_CA, standard deviation score for chronologic age

One of the major problems preventing satisfactory rehabilitation of children after successful RTx is short stature. Many adults who received kidney transplants during childhood have a final height below the 3rd height percentile (1; Hokken-Koelega *et al.*, unpublished manuscript). Much of the growth deficit occurs because of poor growth before RTx, particularly during infancy and while undergoing dialysis (3, 4). Growth rates may improve after RTx, but it seldom leads to sufficient catch-up growth (5). Prednisone therapy might be a major cause of poor growth after RTx. Alternate-day rather than daily administration of prednisone has been reported to have a beneficial effect on growth (6; Hokken-Koelega *et al.*, unpublished manuscript), and the use of CsA instead of Aza may lead to improved growth rates (7, 8). Posttransplant growth may also be influenced by several other factors, such as renal graft function and chronologic age and bone age at the time of RTx (9). Unfortunately, most studies only focus on the effect of one or other specific factor on growth after RTx, not taking into account the complex and probably interrelated effects of various factors combined.

We therefore evaluated, retrospectively, the posttransplant growth of 70 strictly prepubertal children during the first 2 y after RTx, including assessment of the impact of several variables simultaneously. These variables included gender, primary renal disease, chronologic and bone age at RTx, duration of first dialysis period, graft function, and various treatment modalities after RTx.

PATIENTS AND METHODS

From February 1972 to May 1990, 212 pediatric patients younger than 15 y of age received their first functioning renal allograft (RTx) at one of the three pediatric centers involved in this study. This number represents the majority of all Dutch children who underwent first RTx (95% cadaveric) during this period, excluding those with renal allografts that ceased to function within 3 d after RTx. We evaluated the growth data of these patients retrospectively, with the exclusion of 63 patients. Eighteen of these 63 patients had died within 1 y after RTx, six had received androgen therapy before RTx, eight had either cystinosis or oxalosis, the records of 25 patients were incomplete, and six refused to have their data included. For the present study we selected 70 (47 boys and 23 girls) of the remaining 149 patients, all of whom had remained prepubertal (Tanner stage 1) (10) for 2 y after their first RTx.

Data were collected from the start of the first dialysis up to 2 y after the first RTx. The patients had been monitored regularly during this period, and the following items were noted: height; weight; sexual maturation; serum creatinine level; episodes and type of dialysis and number of RTx; type and dose of immuno-suppressive drugs including prednisone regimen; occurrence of acute or chronic rejection episodes (diagnosed by renal biopsy, increased serum creatinine level, fever, hypertension, decreased urine output, or renal scintigraphy); and bone age if appropriate. The primary renal disease and the parents' heights were also recorded. Height had been measured with a Harpenden stadiometer, and expressed in centimeters and hSDS$_{CA}$. Height standards of healthy Dutch children were used as reference data (11). Bone maturation was determined from radiographs of the left hand and wrist using the method of Greulich and Pyle (12). Pubertal maturation was recorded according to Tanner's scale (10). Parent's height served to calculate the target height for each individual patient. Secular trend was taken into account: father's + mother's height ± 12 cm/2, + 3 cm (13). Target height in centimeters was converted into target hSDS$_{CA}$ with Dutch standards for final height (11). We determined the GFR in these children during the 2 y after RTx with the method described by Morris (14): (height in cm × 40, divided by serum creatinine level in μmol/L) and expressed as mL/min/1.73 m^2.

All children received immunosuppressive medication consisting of prednisone and either Aza or CsA. Prednisone administration started on the day of RTx at a dose of 3 mg/kg/d, tapering off to 1 mg/kg/d during the first 3 mo postoperatively. Subsequently, prednisone therapy was reduced to a maintenance dose of 0.15–0.30 mg/kg/d. Two prednisone regimens were used: administration was either daily or on alternate days. Acute rejection episodes were treated with either 20 mg/kg i.v. methylprednisolone on alternate days for a period of 10–14 d or oral prednisone in an initial dose of 200 mg/1.73 m^2, which was reduced every 3 d to taper off to a maintenance dose in the course of 15 d. Until 1984, Aza was given adjuvantly, starting immediately after RTx at a dose of 3 mg/kg/d and tapering off to a maintenance dose of 2 mg/kg/d or less. From 1984, several children received CsA instead of Aza adjuvant to prednisone. CsA was also started the day of RTx at a dose of 14 mg/kg/d, tapering off to a maintenance dose of 7–8 mg/kg/d or even less depending on plasma levels of CsA (desired plasma level of therapeutic CsA from 3 mo after RTx: 30–70 ng/mL).

For each individual patient, we calculated the percentage of time on alternate-day prednisone administration, the cumulative dose of prednisone (mg/kg), the percentage of time on either Aza or CsA treatment, and the total duration (years) of a reduced GFR (<50 mL/min/1.73 m^2) during the 2 y after RTx.

Two-sample t test was used to assess differences between two groups. To study the influence of a number of variables on the change in hSDS$_{CA}$ during 2 y after RTx (ΔhSDS$_{CA}$), we carried out a simple linear regression analysis involving the association between a continuous variable and the ΔhSDS$_{CA}$, whereby each variable was considered singly. To determine the influence on ΔhSDS$_{CA}$ of several variables simultaneously, we then carried out multiple regression analyses. This first involved a stepwise, backward elimination procedure on the variables known at the time of the first RTx [i.e. gender (1 = male), duration of initial dialysis period (years), primary renal disease (1 = urinary tract abnormalities, or renal hypoplasia, or both; 2 = glomerulopathies; 3 = nephrotic syndrome), chronologic and bone age at first RTx (years), hSDS$_{CA}$, and target hSDS$_{CA}$]. Next, the model was extended in a backward selection manner, also stepwise, adding the posttransplant variables [i.e. percentage of time on alternate-day prednisone, cumulative dose of prednisone (counted per 100 mg/kg), length of time (years) that GFR remained below 50 mL/min/1.73 m^2, Aza versus CsA for more than 85% of time (1 versus 0)]; all concerned the first 2 y after RTx.

RESULTS

Clinical data of our 70 prepubertal patients (47 boys and 23 girls) are summarized in Table 1. The primary renal disease consisted of glomerulopathies in 35 patients (50.0%), urinary tract abnormalities and/or renal hypoplasia in 25 patients (35.7%), and nephrotic syndrome in eight patients (11.4%). This information was not available for the remaining two boys (2.9%). Sixty-five children underwent dialysis before their first RTx; 33 boys and 14 girls were on hemodialysis, whereas 11 boys and seven girls had peritoneal dialysis. Five children, three boys and two girls, did not have dialysis before their first RTx. During the 2 y after RTx, 40 children (57%) had stable grafts with a GFR above 50 mL/min/1.73 m^2, whereas 30 children (43%) had deterioration of renal function. For 5 of them (7%), this meant only a temporary decrease of the GFR to less than 50 mL/min/1.73 m^2 with normal values at the end of the 2nd y after RTx; 18 (26%) had progressive graft deterioration to a persistent GFR below 50 mL/min/1.73 m^2, two of whom had a second RTx within 2 y; seven (10%) resumed dialysis after acute progression to graft failure, three of whom also had a second RTx during the first 2 y after RTx.

Growth. Height SDS$_{CA}$ for each individual patient is presented in Figure 1 at initiation of dialysis, at the first RTx, at 12 mo and at 24 mo after RTx in relationship to the mean target

Table 1. Clinical data of 70 prepubertal children

	Boys (n = 47)	Girls (n = 23)
Primary renal disease		
Congenital (urinary abnormalities) (n)	18	7
Acquired (glomerulopathy) (n)	22	13
Nephrotic syndrome (n)	5	3
Unknown (n)	2	0
First dialysis		
Chronologic age in years (range)	7.3 (1.3 to 11.3)	7.4 (3.7 to 11.6)
Duration in years (range)	1.1 (0.2 to 7.4)	0.8 (0.3 to 3.2)
Type		
Hemodialysis (n)	33	14
Continuous ambulatory peritoneal dialysis (n)	11	7
First RTx		
Chronologic age in years (range)	8.0 (2.2 to 12.1)	8.6 (3.0 to 12.0)
Bone age in years (range)	6.5 (2.2 to 11.1)	6.9 (2.9 to 11.2)
Prednisone therapy		
Percentage of time on alternate-day prednisone		
0% (n)	21	16
10–60% (n)	17	3
>60% (n)	9	4
Immunosuppressive therapy		
Percentage of time on aza		
>85% (n)	34	17
20–60% (n)	4	2
0% (n)	9	4
Renal graft function 2 y after RTx		
GFR > 50 mL/min/1.73 m^2*	32	13
GFR < 50 mL/min/1.73 m^2†	12	6

* Including five patients who had a temporary decline in GFR during these 2 y.
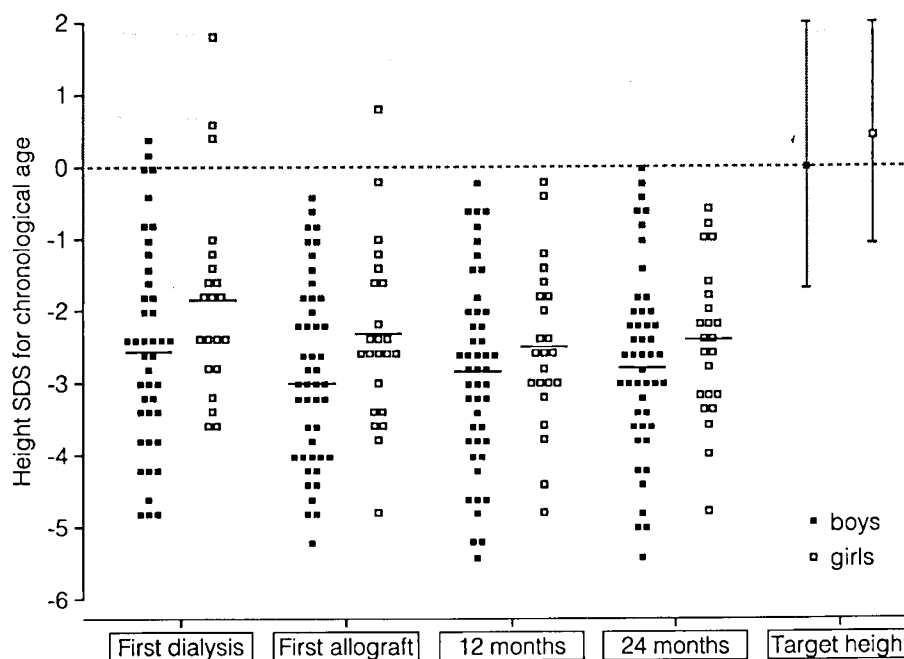
† Mean (range) duration: 1.2 (0.1–2.0) y.

Fig. 1. Individual and mean hSDS$_{CA}$ from first dialysis through 2 y after first RTx and mean (range) target hSDS$_{CA}$ for 70 prepubertal patients. *Dotted area* represents 94% of the healthy Dutch reference population (the area between the 3rd and 97th height percentile for chronologic age).

hSDS$_{CA}$. It appeared that the mean height for all patients was already below the 3rd percentile for height (<-1.88 hSDS$_{CA}$) at the start of the first dialysis. A significant mean decrease of hSDS$_{CA}$ (Wilcoxon's signed rank test: $p < 0.0001$) took place during dialysis, amounting to -0.5 (SD 0.7) for boys and -0.4 (SD 0.5) for girls. Per year, the change was -0.4 SD for both sexes.

At the time of the first RTx, the mean hSDS$_{CA}$ for boys was -3.0 (SD 1.3), and for girls it was -2.3 (SD 1.2). During the next 2 y the mean change in hSDS$_{CA}$ was $+0.3$ (SD 0.8) for boys and -0.1 (SD 1.0) for girls, with only the change in boys being significant ($p = 0.03$). Figure 2 shows the percentage of boys and

girls per change in hSDS$_{CA}$ during 2 y after their first RTx. A change in hSDS$_{CA}$ between $+0.5$ and -0.5 SD was seen in 53% of the boys and 26% of the girls. An increase in hSDS$_{CA}$ over 0.5 SD was found in 32% of the boys and 31% of the girls, whereas a decline over 0.5 SD had occurred in only 15% of the boys but 43% of the girls.

Impact of various factors on posttransplant growth. Simple linear regression analysis revealed a significant negative association between the change in hSDS$_{CA}$ during the 2 y after the first RTx (ΔhSDS$_{CA}$) and the following variables: hSDS$_{CA}$ at the first RTx ($p = 0.0001$), Aza *versus* CsA medication ($p = 0.005$), cumulative dose of prednisone during these two y ($p = 0.04$),
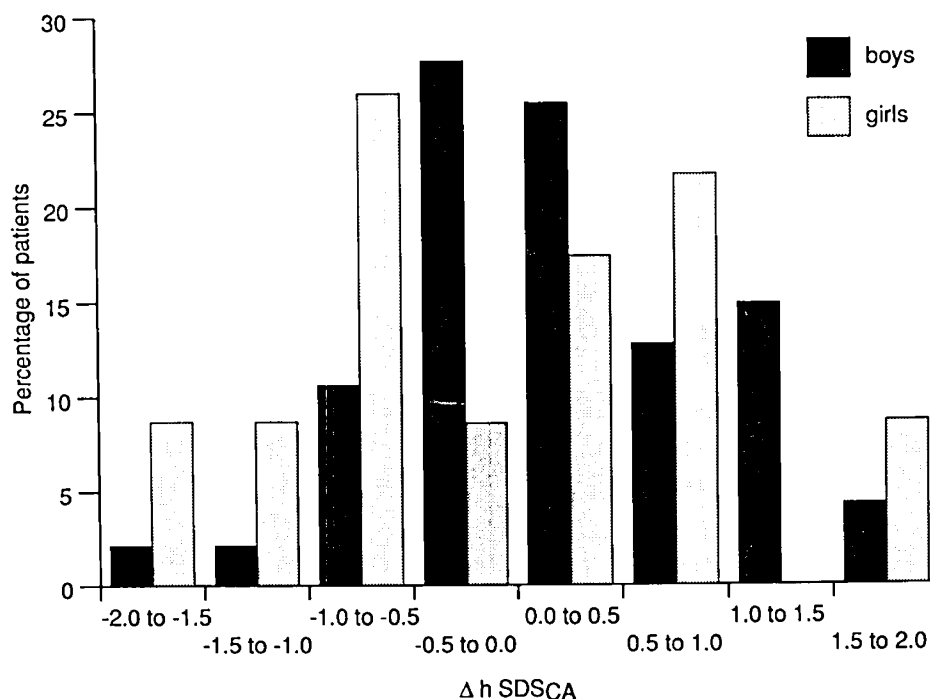

Fig. 2. Percentage of prepubertal boys and girls per change in hSDS$_{CA}$ during 2 y after RTx.

and bone age at the time of the first RTx ($p = 0.02$). A significant positive association was found for the variables: percentage of time on alternate-day prednisone ($p = 0.0003$), and urinary tract abnormalities and/or renal hypoplasia *versus* other renal disease ($p = 0.04$). Factors that proved not to be significant when analyzed individually were gender, target $hSDS_{CA}$, duration of initial dialysis period, age at the first RTx, and duration of GFR less than 50 mL/min/1.73 m².

The backward multiple regression analysis performed on the variables known at the time of the first RTx resulted in a model containing only the $hSDS_{CA}$ at the first RTx. Subsequent, stepwise backward selection including posttransplant variables revealed the following predictive factors: percentage of time on alternate-day prednisone (% AD), the cumulative dose of prednisone during the 2-y study period, Aza *versus* CsA therapy, and duration of a reduced GFR (<50 mL/min/1.73 m²). The results of this multiple regression model, given in Table 2, provided the following equation for predicting the change in height SDS_{CA} ($\Delta hSDS_{CA}$) in prepubertal children during 2 y after their first RTx:

$\Delta hSDS_{CA} = 0.13 - 0.30 \times hSDS_{CA}$ at RTx $+ 0.01 \times \%AD$

$- 0.19 \times$ cumulative prednisone $- 0.43 \times$ Aza therapy

$- 0.28 \times$ years with GFR < 50 mL/min/1.73 m²

The regression coefficient for $hSDS_{CA}$ at RTx was -0.30, indicating that the increase in $hSDS_{CA}$ was smaller when $hSDS_{CA}$ at the first RTx was relatively high. In other words, the children who were relatively tall when undergoing their first RTx had less catch-up growth after RTx than those who were shorter at RTx, whose growth retardation had been more severe. Thus, the change in $hSDS_{CA}$ of two patients, one of whom is 1 $hSDS_{CA}$ shorter at the first RTx than the other one, will be 0.30 SD more for the shorter patient, provided the other factors are equal.

The regression equation for the prediction of the $hSDS_{CA}$ attained 2 y after the first RTx can be derived from the above mentioned regression equation:

Attained $hSDS_{CA} = 0.13 + 0.70 \times hSDS_{CA}$ at RTx $+ 0.01$

$\times \%AD - 0.19 \times$ cumulative prednisone $- 0.43$

$\times$ Aza therapy $- 0.28 \times$ years with GFR

< 50 mL/min/1.73 m₂

The regression coefficient for $hSDS_{CA}$ at the first RTx being $+0.70$ with respect to the $hSDS_{CA}$ attained 2 y later has the following implication. For the same two patients cited above,

Table 2. *Multiple regression analysis on the changes in height SDS_{CA} during 2 y after first renal transplantation in 70 prepubertal patients*

Variable	Regression coefficient	SE	*p* value
Height SDS_{CA} at first RTx	−0.30	0.06	<0.0001
Percentage of time on alternate-day prednisone	0.01	0.00	<0.0001
Cumulative dose of prednisone (per 100 mg/kg)	−0.19	0.08	0.02
Aza *vs* CsA medication	−0.43	0.18	0.02
Duration of reduced graft function (y) (GFR < 50 mL/min/1.73 m²)	−0.28	0.12	0.02

Regression equations: Predicted change in $hSDS_{CA}$ during 2 y after RTx $= 0.13 - 0.30 \times hSDS_{CA}$ at RTx $+ 0.01 \times \%AD - 0.19 \times$ cumulative prednisone $- 0.43 \times$ Aza therapy $- 0.28 \times$ years with GFR < 50 mL/ min/1.73 m²; $hSDS_{CA}$ at 2 y after RTx $= 0.13 + 0.70 \times hSDS_{CA}$ at RTx $+ 0.01 \times \%AD - 0.19 \times$ cumulative prednisone $- 0.43 \times$ Aza therapy $- 0.28 \times$ years with GFR < 50 mL/min/1.73 m².

who differ by 1 $hSDS_{CA}$ at the first RTx, the patient with the most severe growth retardation will be 0.70 SD shorter than the other patient at 2 y after RTx despite better catch-up growth.

The regression coefficient for the percentage of time on alternate-day prednisone was +0.01 which means, for example, that the change in $hSDS_{CA}$ of two patients, one on 80% alternate-day and the other on 0% alternate-day (100% daily) prednisone, will be 0.8 SD higher for the patient with 80% alternate-day prednisone, provided all other factors remain equal.

The regression coefficient for the cumulative dose of prednisone was −0.19, which means that for each additional 100 mg/ kg prednisone administered during the 2-y period, the loss in $hSDS_{CA}$ increased by 0.19 SD.

Aza *versus* CsA treatment had a significantly negative effect on the 2-y posttransplant growth, amounting to an average growth reduction of 0.4 SD for the patient receiving Aza.

The regression coefficient for duration of reduced GFR was −0.28, implying that for each year that the GFR remains under 50 mL/min/1.73 m², the decrease in $hSDS_{CA}$ during 2 y after RTx will amount to 0.3 SD, provided the other factors remain equal.

DISCUSSION

Our study revealed that the mean $hSDS_{CA}$ of the prepubertal study population was already below −1.88 SD when dialysis was initiated. Subsequently, dialysis resulted in a significant decrease in $hSDS_{CA}$, amounting to −0.4 SD per year for boys and girls alike until this process was halted at RTx. As a result, many children had a substantial degree of growth retardation by the time they had their first RTx. During the 2 y after RTx, only 30% of these children had an appreciable catch-up growth (*i.e.* an increase in $hSDS_{CA}$ of more than +0.5 SD). Other studies have also indicated that few children experience a marked catch-up growth after successful RTx (9, 15, 16). The present findings correspond with the results of our previous study, which indicated that 77% of men and 71% of women who had received their first RTx before the age of 15 attained a final height below the 3rd height percentile ($hSDS_{CA} < -1.88$) (Hokken-Koelega *et al.*, unpublished manuscript).

Until now, the variables that might influence growth during the 1st years after RTx were largely unknown (15). Our study has revealed that five variables simultaneously have a significant influence on the 2-y growth after RTx: $hSDS_{CA}$ at the time of the first RTx, percentage of time on alternate-day prednisone, cumulative dose of prednisone, Aza therapy *versus* CsA or combined CsA/Aza treatment, and duration of reduced graft function (GFR < 50 mL/min/1.73 m²).

Our study showed that the posttransplant growth was best in our patients with the lowest $hSDS_{CA}$ at the time of their first RTx. Bosque *et al.* (9) similarly found a significant negative correlation between $hSDS_{CA}$ at the first RTx and the subsequent growth in 46 patients. However, our study also revealed that the better catch-up growth after RTx did not in fact compensate for the severe growth retardation at RTx. Multiple regression analysis showed that $hSDS_{CA}$ at the time of the first RTx has a significant positive effect on the $hSDS_{CA}$ attained 2 y after RTx.

The present study clearly demonstrated that alternate-day prednisone administration has a beneficial effect on growth compared with daily administration, even in the presence of other significant factors. The positive effect of alternate-day prednisone has been reported by others (9, 17), but these studies did not differentiate between the effect of either alternate-day or daily therapy coupled with that of other factors. A recent prospective and controlled study analyzed the effect of alternate-day *versus* daily prednisone therapy on growth during a relatively short period of 14 to 27 mo in a selected group of children with normally functioning renal grafts (6). The authors concluded that the inhibitory effect on growth velocity of a certain cumulative dose of prednisone was significantly less when given on alternate days, without any additional risk of rejection. From

these results together with our present and earlier findings, one might conclude that alternate-day prednisone administration is preferable to daily administration. However, well-controlled, long-term studies are required to verify that the alternate-day regimen does not increase the risk of renal graft deterioration.

Our study revealed that the cumulative dose of prednisone administered during the 2 y after RTx had a significant negative effect on growth during that period even in the presence of other significant factors. The mode of action of steroids in inhibiting growth is still largely a matter for conjecture. We have recently demonstrated that patients with growth retardation after RTx who had received long-term prednisone therapy had significantly lower 24-h plasma growth hormone levels than healthy controls (18). Others have reported that corticosteroids have a direct inhibitory effect on the cartilage, collagen synthesis, and bone matrix formation (19–21), and corticosteroids had a suppressive effect on IGF-I mRNA levels in several tissues (22). Thus, one of the mechanisms involved in growth retardation after RTx might be the prednisone-induced inhibition of local IGF-I gene expression.

Treatment with Aza appeared to have a significantly negative effect on posttransplant growth compared with CsA treatment. It has been reported that CsA therapy allows for decreased dosage of corticosteroids while improving growth rates (7, 8, 23). However, the variables Aza therapy and cumulative dose of prednisone each retained a significantly negative influence on posttransplant growth when regarded simultaneously in the multiple regression model. Thus, the improved growth during CsA treatment is not merely attributable to a reduced cumulative dose of prednisone. It has been reported that the GFR of patients treated with Aza was higher than the GFR of patients on CsA (7), although others have found no significant difference in actual graft survival (23). Additional, well-controlled studies are required to verify that CsA treatment does not lead to premature graft failure.

The multiple regression analysis revealed that persistence of a reduced GFR (<50 mL/min/1.73 m^2) has a significantly negative effect on posttransplant growth. In an earlier study, we found a negative correlation between renal graft function and the serum IGF-binding protein-3 levels (18). Consequently, a reduced GFR together with decreased IGF bioavailability may well play a role in the disappointing growth after RTx.

Gender, primary renal disease, duration of the first dialysis period, chronologic and bone age at the time of the first RTx, and target hSDS$_{CA}$ proved to have no significant effect on the change in hSDS$_{CA}$ after RTx when evaluated simultaneously in the multiple regression analyses.

In conclusion, our study shows that 70% of prepubertal renal allograft patients do not have an appreciable catch-up growth during the first 2 y after RTx. Despite an apparent positive correlation between severe growth retardation at the time of RTx and increased growth immediately after RTx, this increased catch-up growth will not fully compensate for pre-RTx growth retardation. Two years after RTx the height of the children with severe growth retardation at RTx still lagged behind that of children whose growth retardation was less severe at RTx. Consequently, optimization of the hSDS$_{CA}$ at RTx is very important. Recent studies have demonstrated that biosynthetic growth hormone therapy accelerates growth significantly in children with chronic renal insufficiency, resulting in an improved hSDS$_{CA}$ at RTx (24, 25). After RTx, maximum catch-up growth may then be achieved provided the following conditions are met: alternate-day instead of daily prednisone administration, a minimal cu-

mulative dose of prednisone, CsA instead of Aza treatment, and a GFR above 50 mL/min/1.73 m^2.

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