Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients

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Abstract

Aims—To evaluate the efficacy (height velocity (HV), change in height standard deviation score (AHSDS)), and safety (glomerular filtration rate (GFR), incidence of rejection, and calcium and glucose metabolism) of recombinant human growth hormone (rhGH) treatment after renal transplantation.

Design—A two year randomised controlled trial.

Subjects—Fifteen prepubertal and seven pubertal children: mean (SD) age, 13.0 (2.6) and 15.2 (2.4) years, respectively; mean (SD) GFR, 51 (30) and 48 (17) ml/min/1.73 m², respectively. Six prepubertal and three pubertal children were controls during the first year; all received rhGH in the second year.

Results—In the first year, mean (SE) HV and AHSDS in the prepubertal treated group increased compared with controls: 8.1 (0.9) v 3.7 (0.6) cm/year and 0.6 (0.1) v −0.3 (0.2), respectively. In the pubertal treated group, mean (SE) HV and AHSDS were also greater: 10.1 (0.6) v 3.9 (1.3) cm/year and 0.6 (0.1) v −0.1 (0.2), respectively. Comparing all treated and control children, there was no significant change in GFR: treated group, mean (SE) 9.9 (5.4) ml/min/1.73 m² v control group, −1.6 (7.6) ml/min/1.73 m². There were also no differences in the incidence of rejection in the first year: eight episodes in 13 patients v five episodes in nine patients, respectively. Phosphate, alkaline phosphatase (ALP), parathyroid hormone (PTH), and fasting insulin concentrations rose during the first year of treatment, but not thereafter. In the second year of treatment, HV remained above baseline.

Conclusion—Treatment with rhGH improves growth in prepubertal and pubertal children with renal transplants, with no significant change in GFR or the incidence of rejection. Phosphate, ALP, PTH, and insulin increased during the first year of treatment.

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Methods Twenty two children with renal transplants were enrolled into a two year, open labelled, prospective and controlled trial of the use of rhGH. Patients from three paediatric nephrology centres in the UK were stratified according to pubertal stage, and then randomised to rhGH (treatment group) or no treatment (control group) in the first year of the trial, with all children receiving rhGH in the second year. Six children continued on rhGH treatment after completion of the trial; data from these children are also reported.

The children were seen on day 1, day 8, and then at three monthly intervals for two years. On each occasion, height, weight, blood pressure, and blood biochemistry including urea, creatinine, calcium, phosphate, alkaline phosphatase (ALP), intact parathyroid hormone (PTH), glucose, insulin, and glycosylated haemoglobin (HbA1c) were checked. The growth standards of Tanner and Whitehouse were used to calculate height standard deviation score (HSDS). Per cent ideal weight for height (WFH) was calculated six monthly.

For the duration of the trial, the occurrence of adverse events was noted. Every six months, GFR was measured by clearance of inulin, using a constant infusion and urine collections. A rejection episode was defined as an episode of transplant dysfunction treated with three days of high dose oral prednisolone. The diagnosis was made by the managing clinician.
Recombinant human growth hormone (Genotropin; Pharmacia and Upjohn, Stockholm, Sweden) at a dose of 0.14 IU (0.05 mg)/kg/day (equivalent to a dose of 4 IU/m2/day) was given as a subcutaneous injection each evening by the child or a parent.

INCLUSION CRITERIA
Children were considered eligible for entry to the trial if they fulfilled the following criteria: height less than the third centile for age and sex or a height velocity (HV) < 25th centile; normal thyroid function. All had been transplanted for at least one year, and had a minimum calculated GFR of 20 ml/min/1.73m2.11

EXCLUSION CRITERIA
Children were excluded from the trial for the following reasons: HV > 75th centile during the preceding six months, treatment with any form of growth hormone in the past year, a previous malignancy, a severe congenital abnormality, diabetes mellitus, or uncontrolled renal bone disease.

The prepubertal group was defined by a testicular volume of < 4 ml in boys and breast development less than Tanner stage B2 in girls.12 Children who were in the early stages of puberty were enrolled into the pubertal group (testicular volume ≥ 4 ml and ≤ 10 ml, breast stage B2 or B3).

PATIENTS
Fifteen prepubertal (two girls) and seven pubertal patients (two girls) were enrolled and randomised to receive either rhGH or no rhGH in the first year. Nine prepubertal and four pubertal children received rhGH in the first year (treatment group); all 22 children received rhGH in the second year.

In the prepubertal group, the mean age was 13.0 (range, 9.4–16.5) years and mean GFR was 51 (range, 13–117) ml/min/1.73m2. The respective values in the pubertal group were 15.2 (range, 12.4–19.8) years and 48 (range, 23–78) ml/min/1.73m2. Eleven of the prepubertal children had renal failure secondary to a congenital structural problem, two had glomerulonephritis, one cystinosis, and the other had atypical haemolytic uraemic syndrome. In the pubertal group, three had congenital structural problems, two glomerulonephritis, one congenital nephrotic syndrome, and one had haemolytic uraemic syndrome. HSDS at baseline, and HV and height velocity standard deviation score (HVSDS) during the preceding year are given in tables 1 and 2. Immunosuppression consisted of azathioprine (60 mg/m2), prednisolone (10 mg/m2 on alternate days), and cyclosporin A. Cyclosporin A dose was adjusted to maintain plasma trough levels between 50 and 150 ng/ml.

FOLLOW UP DATA
Fourteen children have been followed up for two years, three for three years, two for five years, and one child has been treated for six years. HV and calculated GFR were measured during this time. In addition, the first year of rhGH treatment in all patients was compared with the growth rate during the preceding year. Age, pretreatment HV and HSDS, GFR, and steroid dose were correlated with the increase in HV and HSDS during the first year of treatment.

STATISTICAL ANALYSIS
Results are expressed as mean (range) or mean (SD). Within and between group results were compared using the paired or unpaired Student’s t test, respectively. Comparison of change within the treatment and control groups was made by calculating and comparing the mean (SE) change. Frequencies were compared using the χ2 test. Analysis of multiple results within the same group over time was performed by analysis of variance (ANOVA). Correlations were performed using Pearson’s correlation coefficient, and regression by both single and multiple linear regression analyses. Significance was set at a p value of < 0.05.

Results
TREATMENT GROUP (NINE PREPUBERTAL AND FOUR PUBERTAL CHILDREN)
Two prepubertal children stopped rhGH; one child returned to dialysis after 11 months, the other developed glucose intolerance after nine months of treatment. Two children stopped treatment during the second year; one prepu-
betal child had started the trial with poor graft function and received a second graft after 18 months of rhGH, the other pubertal child had an increase in creatinine.

CONTROL GROUP (SIX PREPUBERTAL AND THREE PUBERTAL CHILDREN)

One pubertal child was withdrawn after 18 months because of a poor response to six months of rhGH treatment.

GROWTH

Prepubertal group (n = 15)

During the first year of the study, HV and HVSDS were greater in the treatment group than the control group (table 1). The mean (SE) increase in HSDS (ΔHSDS) during the first year of study was 0.6 (0.1) in the treatment group and −0.3 (0.2) in the control group; p < 0.001 (table 2).

In the treatment group, there was no difference between ΔHSDS in the first and second years of treatment; 0.6 (0.1) v 0.4 (0.2), respectively (p = 0.34). HV and HVSDS were lower in the second year compared with the first year of treatment (table 1). The increase in mean (SE) HSDS during the second year in the treatment group was greater than that in the first year in the control group (0.4 (0.2) v −0.3 (0.2); p = 0.003), but HV and HVSDS were not significantly different (p = 0.16 and 0.09, respectively). In the control group, HV, HVSDS, and ΔHSDS were greater in the second year of rhGH treatment than in the first year (tables 1 and 2).

Pubertal group (n = 7)

The results in the pubertal group were similar to those in the prepubertal group; however, the numbers of children in the treatment and control groups were small. During the first year of the trial, HV and ΔHSDS were significantly greater in the treatment group than the control group; the corresponding p value for HVSDS was p = 0.06 (tables 1 and 2).

In the treatment group, HV, HVSDS, and ΔHSDS remained above pretreatment values in the second year of the study, but were lower than the respective values in the first year of the trial. Comparing the first and second year data in the control group, HV, HVSDS, and ΔHSDS were greater in the second year than in the first year, but the values were not significant (tables 1 and 2).

Pooled follow up data for all prepubertal children during rhGH treatment

When data are pooled for all 15 prepubertal children during their first year of rhGH treatment, mean HV increased significantly from 3.8 (range, 0.8–6.9) cm/year in the year before treatment to 8.2 (range, 3.0–12.5) cm/year; p < 0.001. The corresponding values for HVSDS were −1.1 (range, −4.7 to 2.1) and 4.4 (range, −2.7 to 13.6; p < 0.001). Mean ΔHSDS decreased from −3.2 (range, −5.1 to −2.0) to −3.5 (−5.8 to −1.3; p = 0.015) in the year before treatment, and subsequently rose to −2.9 (−5.0 to −1.3) after one year of treatment (p < 0.001).

Ten prepubertal children received rhGH for at least two years. In these children, ΔHSDS increased from −3.4 (−5.8 to −1.9) on day 1, to −2.4 (−4.4 to −1.2) after two years (p = 0.002). Mean HV was 3.9 (range, 0.8–6.9) cm/year in the year before treatment, 8.2 (range, 3.0–10.7) cm/year in the first year (p < 0.0002 compared with the previous year), and 6.1 (range, 0.1–8.8) cm/year during the second year (p = 0.012 compared with the year before treatment). The mean gain in height was 14.8 (range, 3.1–18.5) cm in two years. Three children received three years of rhGH treatment; mean height gain was 22.1 (range, 21.8–22.4) cm in three years. One child received rhGH for five years and another for six years; HVSDS remained above pretreatment values during this time.

Pooled follow up data for all pubertal children during rhGH treatment

Considering all seven pubertal children, mean HV increased from 4.2 (range, 1.3–8.1) cm/year in the year before treatment to 8.4 (range, 1.8–11.7) cm/year (p < 0.05) during the first year of treatment. Mean ΔHSDS was −2.3 (range, −3.8 to −1.2) one year before starting treatment, −2.5 (range, −4.5 to −1.6) at the start of treatment, and −2.0 (range, −3.7 to −0.9) after one year (p < 0.05). Five of the seven patients completed the study, but elected to stop treatment. Four children received two years of rhGH: mean HV was 5.2 (range, 3.5–8.1) cm/year before treatment, 9.3 (range, 5.3–11.7) cm/year in the first year of treatment, and 5.8 (range, 4.1–8.7) cm/year in the second year of treatment, values very similar to the prepubertal group. The average height gain during two years of rhGH was 15.0 (range, 9.5–19.3) cm.

Regression analysis

There was no significant difference in the increase in HSDS and HV in the first year of treatment between the prepubertal and pubertal groups. Combining the prepubertal and pubertal groups, HV before and during rhGH was related to age (r = −0.417; p = 0.05 and r = −0.463; p = 0.03, respectively). Multiple regression analysis revealed that prednisolone dose (p = 0.028) and age (p = 0.049) were the strongest negative predictors of ΔHSDS. Using single regression analysis, HV during treatment was positively correlated with GFR (r = 0.429; p = 0.016), but this relation became non-significant when the effects of age and prednisolone dose were taken into account. There was no significant association between ΔHSDS and HSDS on day 1 (r = 0.034) or between ΔHSDS and HV (r = 0.265) before treatment.

Weight for height

At the start of treatment, all children had a WFH > 100%. The two lowest values (105% and 108%) were in the two children who received no prednisolone treatment. Mean WFH decreased during the first year of treatment from 133% (range, 105–171%) at the start of treatment, to 125% (range,
99–152%) at six months (p < 0.001), and 122% (range, 96–152%) at one year (p < 0.001). WFR remained significantly reduced after two years 120% (range, 88–168%; p = 0.016).

RENAL FUNCTION

Results for the prepubertal and pubertal children were combined; GFR at baseline was comparable in the treatment and control groups (p = 0.12). The mean (SE) change in GFR during the first year was 9.9 (5.4) ml/min/1.73m² in the treated group (n = 12) and −1.6 (7.6) ml/min/1.73m² in the control group (n = 9; p = 0.22). One child in the treatment group was withdrawn during the first year because of graft failure. Setting his GFR to zero at the one year visit does not significantly alter the change in GFR during the first year: treated group mean (SE) GFR 7.2 (6.0) ml/min/1.73m² (p = 0.36).

Individual GFR values for all children during their first year of rhGH treatment are shown in fig 1. Mean GFR increased significantly during rhGH treatment: 49 (range, 13–117) ml/min/1.73m² on day 1 and 58 (range, 14–133) ml/min/1.73m² after six months (n = 22; p = 0.01). In those children who completed a full year of rhGH, GFR remained higher at one year; 51 v 59 ml/min/1.73m² (n = 19; p = 0.04). However, if a value of zero is included for the child who lost his graft, then the change in GFR becomes non-significant (n = 20; p = 0.12). There was no further change in GFR during the second year of rhGH treatment. Calculated GFR in the children who continued on treatment after the study was complete did not change (data not shown).

Mean serum creatinine in the treated and control groups did not differ at baseline: control group, 100 (range, 49–152) µmol/l and treated group, 114 (range, 46–220; p = 0.46). The mean (SE) change in creatinine during the first year appeared to be greater in the treated group (30.1 (11.7) µmol/l) than in the control group (3.8 (6.2) µmol/l), but was not significantly different (p = 0.11). Mean creatinine at one year in the treated group was 146 (range, 64–317) µmol/l (p = 0.013 compared with day 1) and did not increase further during the second year of treatment; mean creatinine at two years was 146 (range, 70–402) µmol/l. Urea decreased slightly after one week of rhGH treatment, but was unchanged thereafter (data not shown).

Presumed rejection episodes

In the first year of the trial there were eight presumed rejection episodes in 13 patients in the treatment group and in nine patients in the control group (p > 0.10). In the control group, there were no differences between the numbers of episodes in the first and second years of the trial; five episodes in nine patients in each year. Combining the data from all 22 children, there were 15 episodes in 22 patients in the first year of treatment, which was no different from the year before rhGH treatment (11 episodes in 22 patients; p > 0.10).

ADVERSE EVENTS

A 10 year old girl had raised fasting glucose, insulin, and HbA1c concentrations after nine months of rhGH treatment. These values returned to normal when rhGH was stopped. Several years before, while on dialysis, she had pancreatitis and required a partial pancreatectomy. Glucose tolerance tests before and after withdrawal from the trial were normal. She went on to develop insulin dependent diabetes, and chose to restart rhGH treatment once established on insulin replacement.

Table 3 Indices of calcium and glucose metabolism in the treatment and control groups

<table>
<thead>
<tr>
<th>Control group</th>
<th>Normal range</th>
<th>Day 1</th>
<th>Day 8</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.10–2.60</td>
<td>2.43 (0.09)</td>
<td>2.45 (0.04)</td>
<td>2.44 (0.08)</td>
<td>2.46 (0.08)</td>
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<tr>
<td>Phosphate (mmol/l)</td>
<td>0.8–1.50</td>
<td>1.23 (0.23)</td>
<td>1.29 (0.21)</td>
<td>1.20 (0.23)</td>
<td>1.32 (0.16)</td>
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</tr>
<tr>
<td>ALP (units/l)</td>
<td>130–520</td>
<td>231 (81)</td>
<td>212 (89)</td>
<td>240 (145)</td>
<td>214 (126)</td>
<td></td>
</tr>
<tr>
<td>PTH (ng/l)</td>
<td>&lt; 65</td>
<td>43.7 (35.3)</td>
<td>64.6 (48.1)</td>
<td>69.0 (46.0)</td>
<td>61.1 (44.9)</td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>2.5–5.3</td>
<td>5.0 (0.6)</td>
<td>4.7 (0.8)</td>
<td>5.0 (0.8)</td>
<td>5.0 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Insulin (units/l)</td>
<td>3–17</td>
<td>12.7 (6.1)</td>
<td>13.2 (4.8)</td>
<td>21.2 (19.8)</td>
<td>18.8 (15.2)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>2.8–4.9</td>
<td>4.7 (0.9)</td>
<td>4.9 (1.1)</td>
<td>4.5 (1.2)</td>
<td>4.9 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Day 1</th>
<th>Day 8</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>18 months</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.39 (0.14)</td>
<td>2.42 (0.16)</td>
<td>2.40 (0.17)</td>
<td>2.41 (0.14)</td>
<td>2.51 (0.16)</td>
<td>2.43 (0.08)</td>
<td>2.40 (0.21)</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.35 (0.39)</td>
<td>1.39 (0.35)</td>
<td>1.63 (0.35)**</td>
<td>1.55 (0.21)*</td>
<td>1.57 (0.27)*</td>
<td>1.49 (0.28)</td>
<td>1.44 (0.31)</td>
</tr>
<tr>
<td>ALP (units/l)</td>
<td>201 (80)</td>
<td>182 (44)</td>
<td>313 (89)**</td>
<td>309 (87)**</td>
<td>309 (87)**</td>
<td>275 (77)**</td>
<td>236 (72)</td>
</tr>
<tr>
<td>PTH (ng/l)</td>
<td>38.1 (15.2)</td>
<td>37.1 (24.7)</td>
<td>50.8 (29.7)</td>
<td>58.1 (39.4)*</td>
<td>61.7 (35.5)</td>
<td>50.7 (24.9)</td>
<td>58.6 (36.0)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.8 (0.9)</td>
<td>5.5 (0.7)</td>
<td>5.3 (0.8)</td>
<td>4.8 (0.6)</td>
<td>5.0 (1.2)</td>
<td>5.0 (0.7)</td>
<td>4.6 (0.6)</td>
</tr>
<tr>
<td>Insulin (units/l)</td>
<td>15.0 (7.8)</td>
<td>38.9 (30.7)*</td>
<td>36.6 (30.3)*</td>
<td>24.4 (12.4)*</td>
<td>18.1 (10.2)</td>
<td>36.2 (23.9)</td>
<td>18.9 (7.4)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.4 (0.8)</td>
<td>–</td>
<td>4.3 (1.0)</td>
<td>4.4 (0.9)</td>
<td>4.4 (1.1)</td>
<td>4.8 (0.8)</td>
<td>4.6 (0.8)</td>
</tr>
</tbody>
</table>

All values except normal ranges are mean (SD).

*p < 0.05, **p < 0.01 compared with day 1.
A 13 year old boy in the control group developed worsening of a pre-existing idiopathic scoliosis during rhGH treatment, which required surgical correction the following year.

RENA L OSTEOODYSTROPHY
Mean serum calcium, phosphate, ALP, and PTH are shown in table 3. Phosphate, ALP, and PTH increased significantly during the first year of rhGH treatment, but did not change significantly thereafter. No child developed overt renal osteodystrophy.

GLUCOSE
Glucose, insulin, and Hba1c values are shown in table 3. In the treatment group, there was a trend for glucose to increase after one week (p = 0.10), but not thereafter. When the results for all children during rhGH treatment were considered, there was a significant increase in glucose after one week: 4.8 (0.9) on day 1 and 5.4 (0.7) on day 8 (p < 0.005). Fasting insulin was raised in the treatment group after one week of rhGH treatment and remained so until six months, returning toward baseline thereafter. Hba1c was unchanged in the treatment group.

Discussion
This is one of the few controlled trials of rhGH treatment in children with renal transplants to date. This group of children were a subgroup of a large multicentre European study. We have established that rhGH improves growth in both prepubertal and pubertal patients with transplants, that the growth response was equal in the two groups, and that improved growth persisted during the second year of treatment. Comparing the control and treatment groups, there was no apparent adverse effect on graft function.

There are several possible mechanisms whereby rhGH or its mediator, insulin-like growth factor-I (IGF-I), might affect graft function: (1) rhGH increases renal plasma flow and GFR in adults with normal renal function; (2) there are known interactions between rhGH and the immune system, which could potentially cause an increase in the rate of rejection episodes; and (3) rhGH could have a direct effect on the kidney, because there are growth hormone receptors on mesangial cells and IGF-I receptors on proximal tubular and mesangial cells. Because of the relation between rejection episodes and GFR, it is very difficult to study the effects of rhGH on these parameters in isolation.

We have reported previously that children with renal transplants respond to rhGH with a transient increase in GFR, similar to the normal adult kidney. In renal impairment, an increase in GFR might hasten the progression of decline in GFR, the so called hyperfiltration theory. There is no evidence that rhGH adversely affects GFR in children with chronic renal failure, but few studies of rhGH in renal transplantation have formally assessed GFR. Most studies report changes in creatinine or calculated GFR, and an analysis of these trials has been inconclusive. Our data suggest that two years of rhGH treatment does not adversely effect graft function.

However, two children were withdrawn from the study because of a deterioration of renal function. For one patient there was suspicion of non-adherence to immunosuppression, while the other child had an acute rejection episode after six months of treatment. His GFR at one year was little changed from baseline, but one week later he had a further increase in creatinine and was withdrawn from the study. A third child received a second renal transplant after 18 months of rhGH. His renal function had shown a gradual deterioration before and during the trial. The small number of patients, the variability of the clinical course after transplantation, and the expected decline in graft function over time hamper interpretation of the data.

There was no apparent untoward effect of rhGH on the incidence of acute rejection. Some reports suggest that rhGH does not affect acute rejection, while others suggest that it does. Biopsy proven, acute rejection has been documented in several children at varying intervals after starting rhGH treatment. None of these were controlled trials. One study suggests that the risk of rejection is increased by rhGH, but only in children who have had rejection episodes before treatment. In the first year of rhGH treatment, seven of our patients had 15 presumed rejection episodes; all but one had suffered presumed rejection episodes in the previous year.

The incidence of rejection episodes in our study is higher than other studies. This is explained partly by the fact that these were presumed and not biopsy proven episodes and, therefore, likely to be an overestimation. Several patients had chronic rejection at the start of treatment, and other studies report increases in creatinine during rhGH when there is biopsy proven, chronic rejection. It is difficult to determine whether rhGH has decreased GFR, if there has been an increase in muscle bulk, or if this is the natural progression of chronic rejection. A recent study of mixed lymphocyte cultures using lymphocytes from paediatric renal transplant recipients and donor cells, showed that overall, the addition of rhGH to the culture had little effect of acute rejection, while others suggest that it does. Biopsy proven, acute rejection has been documented in several children at varying intervals after starting rhGH treatment. None of these were controlled trials. One study suggests that the risk of rejection is increased by rhGH, but only in children who have had rejection episodes before treatment. In the first year of rhGH treatment, seven of our patients had 15 presumed rejection episodes; all but one had suffered presumed rejection episodes in the previous year.

The best response to rhGH was seen in the youngest children and in those on the least steroid, with the strongest predictor being the dose of prednisolone (p = 0.029). Growth in children with renal transplants, who are not on rhGH, has been correlated with age, GFR, and with steroid treatment. Children on alternate day steroids grow better than those on daily steroids, and peak height velocity during puberty in patients with renal transplants is inversely correlated with steroid dose, so that the relation between response to rhGH and steroid dose is not surprising. In another post-transplant study, the change in HSDS was...
greater than 0.4 after one year of rhGH treatment in five of five children not receiving steroids and one child on alternate day steroids, but was only −0.2 (range, −0.6 to 0.3) in 11 children on daily steroids. Mean creatinine was the same in both groups. All of our patients were receiving alternate day steroids.

Whether rhGH benefits final height, particularly if it is not started until puberty, has yet to be determined. In renal failure, puberty is delayed and the magnitude of the pubertal growth spurt is attenuated.\(^{25}\) Puberty would seem to be an appropriate time to use rhGH, to induce or mimic the endogenous growth spurt, but there is concern that treatment might shorten the duration of the pubertal growth spurt.\(^{35}\) Some reports have suggested that this might be the case in children with renal transplants who receive rhGH,\(^ {31,32}\) while others have demonstrated a substantial increase in height during adolescence.\(^ {3,20}\) There was no undue advancement in bone age in our study (data not shown), nor in other reported studies.\(^ {20}\)

The increase in HSDS was similar in the prepubertal and pubertal treatment groups in our study, with little or no change in HSDS in either of the control groups. However, longer follow up will be necessary to determine if there is a positive effect on final adult height.

ALP, serum phosphate, and PTH increased during treatment. rhGH increases phosphate reabsorption by the renal tubule, and the increase in serum phosphate stimulates PTH.\(^ {35}\) It is important that PTH is monitored regularly during rhGH treatment. There is a concern that rhGH treatment might be associated with an increase in the incidence of slipped capital femoral epiphyses, avascular necrosis of the femoral head, or worsening renal osteodystrophy in children with renal failure.\(^ {31}\) Routine hip x-rays were not performed in our study, but no child developed overt renal osteodystrophy.

One of the patients developed glucose intolerance during the study. This is a recognised complication of acromegaly.\(^ {39}\) Patients with renal disease have peripheral resistance to the actions of insulin,\(^ {31}\) which is aggravated in patients who have received transplants by the use of corticosteroids.\(^ {30}\) Glucose intolerance during rhGH treatment after transplantation has been reported previously.\(^ {30}\) Our patient had undergone a partial pancreatectomy, which might have been a contributing factor. For the group as a whole, the increases in fasting glucose and insulin were transient, and during two years of rhGH treatment there was no increase in HbA1c. There would appear to be no longer term adverse effect on glucose tolerance.

In summary, rhGH improves short term growth in prepubertal and pubertal children with renal transplants compared with controls. Mean HV during the second year of rhGH treatment remained above the baseline value in the prepubertal group. In both groups, the approximate height gain was 15 cm after two years of rhGH treatment. There was no increase in the incidence of rejection episodes. There was a significant increase in GFR during the first six months of treatment, but not thereafter. With continued use of rhGH, HVSDS reduces towards baseline, but growth can remain above pretreatment values for up to six years.

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