Efficacy of Recombinant Human Growth Hormone in Pediatric Renal Transplantation Patients after Withdrawal of Steroid Therapy: Report of Two Cases

Osamu Motoyama,1* Akira Hasegawa,2 Mari Satoh,1 Yukari Shigetomi,1 and Takehiro Ohara2

1First Department of Pediatrics and 2Department of Nephrology, Toho University School of Medicine, Tokyo, Japan

The effects of recombinant human growth hormone (rhGH) were examined in 2 girls without any endocrine abnormalities who showed growth retardation after renal transplantation. After transplantation they received methylprednisolone, which was discontinued 5 years before (in one child), and 3 months after (in the other child) the start of rhGH treatment. The patients received cyclosporine, mizoribine, and azathioprine as immunosuppressive therapy before and during rhGH therapy. 1.0 IU/kg per week divided into 6 doses administered subcutaneously. Growth evaluation on the basis of height standard deviation score (SDS) and growth velocity SDS demonstrated catch-up growth in both cases. Skeletal maturation did not proceed, and their pubertal stage remained unchanged during rhGH treatment. In both cases, renal function was stable and no adverse reaction was noted during rhGH treatment.

Clin Exper Nephrol 1998;2:162-165

Key words: renal transplantation, recombinant human growth hormone, growth retardation, children, steroid withdrawal

Retarded growth in children after transplantation remains a significant clinical problem.1 The growth rates of children with well-functioning grafts, who are receiving relatively low doses of glucocorticosteroids, generally increase during the first 2 years after transplantation and subsequently decline.2 Recent advances in the understanding of growth hormone, insulin-like growth factor (IGF), and IGF-binding protein have contributed to the investigation of growth failure in children after renal transplantation. The use of recombinant human growth hormone (rhGH) may overcome growth-inhibiting factors. Although many studies have examined the effect of rhGH therapy in children with functioning renal grafts, there are few studies on rhGH therapy for children with transplants after steroid withdrawal.2 Here, we report our clinical experience with rhGH in children with renal transplants who received immunosuppressive therapy without steroids.

CASE REPORTS

The 2 girls described here were of normal weight and length at birth. After undergoing peritoneal dialysis since infancy, they received renal transplantation from one haplo-identical, living, related donor. The provocation test for growth hormone secretion, done 1 month (patient 1) and 10 months (patient 2) before the start of rhGH therapy, showed normal secretion of growth hormone (Table 1). At the same time, the response of gonadotropin to luteinizing hormone-releasing hormone was measured (Table 2).

Medical History
Case 1
A 9-year-old girl with a hypoplastic kidney underwent renal transplantation at the age of 2 years. Height at the time of transplantation was 74 cm (−5.5 SD). She received an immunosuppressive regimen with cyclosporine, mizoribine, and methylprednisolone. The postoperative course was uneventful. Two years after transplantation, the methylprednisolone was discontinued. Twice, at 3 years, and again at 7 years after transplantation, histopathologic findings of routine serial graft biopsies revealed acute rejection,
Table 1. Peak values of serum growth hormone (GH) level (ng/mL) after provocation test in children with renal transplants.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pharmacologic stimulation</th>
<th>Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arginine</td>
<td>Insulin</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>18</td>
</tr>
</tbody>
</table>

*Mean GH level was calculated from GH levels examined every 20 minutes over 3 hours after the patients fell asleep. ND, not done.

Table 2. Baseline and peak values of gonadotropin after luteinizing hormone-releasing hormone administration in children with renal transplants.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>LH (mIU/mL)</th>
<th>FSH (mIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak</td>
</tr>
<tr>
<td>1</td>
<td>0.3</td>
<td>7.7</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>20.6</td>
</tr>
</tbody>
</table>

LH, luteinizing hormone; FSH, follicle-stimulating hormone.

but clinically the patient showed no symptoms of rejection, and laboratory tests showed no abnormalities. Each time, she was given a high dose of methylprednisolone by bolus injection for 3 consecutive days to prevent rejection, but maintenance methylprednisolone therapy was not administered. The increment in the growth curve and breast development was judged to be the onset of pubertal growth spur.

Case 2
A 10-year-old girl with congenital nephrotic syndrome underwent renal transplantation when she was 5 years old. Height at the time of transplantation was 83 cm (~7.4 SD). She had no rejection episode. She was given maintenance immunosuppressive therapy with methylprednisolone (3 mg every second day), cyclosporine, mizoribine, and azathioprine from the renal transplantation to 3 months after the start of rhGH treatment. Three months after the start of rhGH treatment, methylprednisolone was discontinued. During the 10 months before the start of rhGH, leuprolrelin acetate (30 to 70 μg/kg) was given by subcutaneous injection every 28 days to prolong the period of pubertal growth.

Growth Evaluation
The rhGH (somatropin provided by Serono Japan, Tokyo, Japan) was given at a dose of 1.0 IU/kg per week given as a subcutaneous injection for 6 evenings each week. Growth evaluation was expressed as height standard deviation score (SDS) and growth velocity SDS for chronologic age calculated from the growth curve for Japanese children: height SDS = (height of the patient – mean height for girls of the same age)/height SD for girls of the same age; growth velocity SDS = (height gain per year of the patient – mean height gain per year for girls of the same age)/height gain SD for girls of the same age; bone age was evaluated using the Japanese version of the TW 2 method (RUS score). Pubertal status was determined using Tanner’s staging system.

Height was 124.5 cm (~1.5 SD) in patient 1 and 118.3 cm (~3.4 SD) in patient 2 at the start of rhGH therapy. Growth evaluation was performed 12 months after the initiation of rhGH therapy in patient 1, and after 16 months in patient 2. During therapy with rhGH, the growth curve (Fig. 1) indicated catch-up growth and height SDS, growth velocity and growth velocity SDS increased in both patients. The ratio of bone age to chronologic age was decreased (Table 3).

The predicted adult height based on bone age was 152.0 cm for patient 1 and 144.8 cm for patient 2 at the start of rhGH treatment. After rhGH treatment, their predicted adult heights increased to 152.9 cm for patient 1 and to 150.4 cm for patient 2. Conversely, their predicted height based on parental height was 160.5 ± 8 cm for patient 1, and 150.5 ± 8 cm for patient 2. Serum concentrations of IGF-1 (ng/mL), measured by radioimmunoassay after acid-ethanol extraction, were 400, 670, and 490, and 290, 500, and 650, for patient 1 and 2 at the start of rhGH treatment, after 1 month of treatment, and after 1 year of treatment, respectively. No change of pubertal stage was observed during rhGH therapy (Table 3). Neither of the patients had started menstruation at the last evaluation. Serum levels of follicle-stimulating hormone increased 6 months after rhGH therapy was started in patient 1, while estradiol levels (pg/mL) were < 10, 21.6, and 45.5 at the start of rhGH treatment, after 6 months of treatment, and after 1 year of treatment, respectively. Serum levels of estradiol remained at less than 10 pg/mL throughout rhGH treatment in patient 2.

Neither patient developed signs of rejection during therapy with rhGH. No changes in serum creatinine levels, other biochemical indicators, or thyroid function were observed during the rhGH therapy. Neither patient developed anti-growth hormone antibody.

DISCUSSION

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 the growth hormone, inhibition of IGF-1 bioactivity, alteration in IGF-1 binding protein, and direct effect on the skeletal tissue matrix. The effects of the