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ORIGINAL ARTICLE

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Growth hormone for children with chronic renal failure and on dialysis

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Abstract We studied all children with CRF who received recombinant human growth hormone (rhGH) for more than a year (mean±SD duration of therapy 3.7±2.5 years) over an 11-year period. There were 32 children. Twenty-one children were conservatively managed, with a mean glomerular filtration rate (GFR) of 24±12 mL min^{-1}/1.73 m^2 at the start of rhGH. Their height standard deviation score improved from −2.5±1.4 to −2.1±0.7 at 1 year (P=0.3), −2.0±0.7 at 2 years (P=0.01), and −1.6±0.6 at 3 years (P=0.001). After that there was no improvement. Eleven children were on dialysis, six on haemodialysis (HD) and five on peritoneal (PD). Ht SDS improved from −2.7±0.5 to −2.3±0.5 at 1 year (P=0.02). Thereafter there was no further improvement. RhGH was stopped because of transplantation in 29 patients at a mean±SD age of 12.1±4.0 years. Mean Ht SDS was −1.8±0.8 at transplant and there was no change over the following 5 years. In conclusion, treatment with rhGH resulted in improvement in Ht SDS in conservatively managed CRF for up to 3.0 years and for 1 year in children on dialysis. Discontinuation of rhGH after transplantation resulted in little change in Ht SDS.

Keywords Chronic renal failure · Dialysis · Growth · Growth hormone

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Introduction

There are many reports demonstrating the short-term effectiveness of growth hormone (rhGH) in children with chronic renal failure (CRF) and on dialysis [1, 2, 3]. Potential predictors of growth response include genetic target height and residual renal function while treatment efficacy is inversely correlated with age and baseline height velocity [4]. More recently, benefits have been demonstrated in the longer-term [5]; height at 18 years of age in patients who had received prior rhGH was greater than a group who had not received rhGH [6]. However, a continuing improvement in Ht SDS after stopping rhGH has also been demonstrated [7]. RhGH has been used increasingly in post-transplant patients and has been shown to be effective and safe [8].

We report our use of rhGH in children with CRF over an eleven-year period. We hope that this will add to the body of literature on this subject.

Patients and methods

Patients

Unit policy is to offer rhGH at a dose of 28 IU m^{-2} $week^{-1}$, given by daily subcutaneous injection, to children of all ages with a Ht SDS more than 2SD below the mean and a height velocity (HV) SDS less than the 25th centile. This is after adequate nutrition has been established, metabolic abnormalities corrected, and dialysis adequacy ensured. Nutritional adequacy was defined as that providing 100% of the estimated average requirement for energy for chronological age, and at least 100% of the reference nutrient intake for protein for height age [9]. Management policy included maintaining the plasma phosphate below the 50th centile for age using calcium carbonate, and PTH within the normal range as far as possible by using, in addition, the lowest possible dose of activated vitamin D. Strict attention was also paid to maintaining the acid–base balance and haemoglobin within the normal range as far as possible. Salt supplements were used in the majority. Dialysis adequacy was assessed by Kt/V, well-being, and growth.

The dose of rhGH was adjusted according to surface area approximately annually. Insulin-like growth factor (IGF)-I levels were not monitored (to document compliance). The dose was not increased above 30 IU m^{-2} $week^{-1}$ even if response was poor.

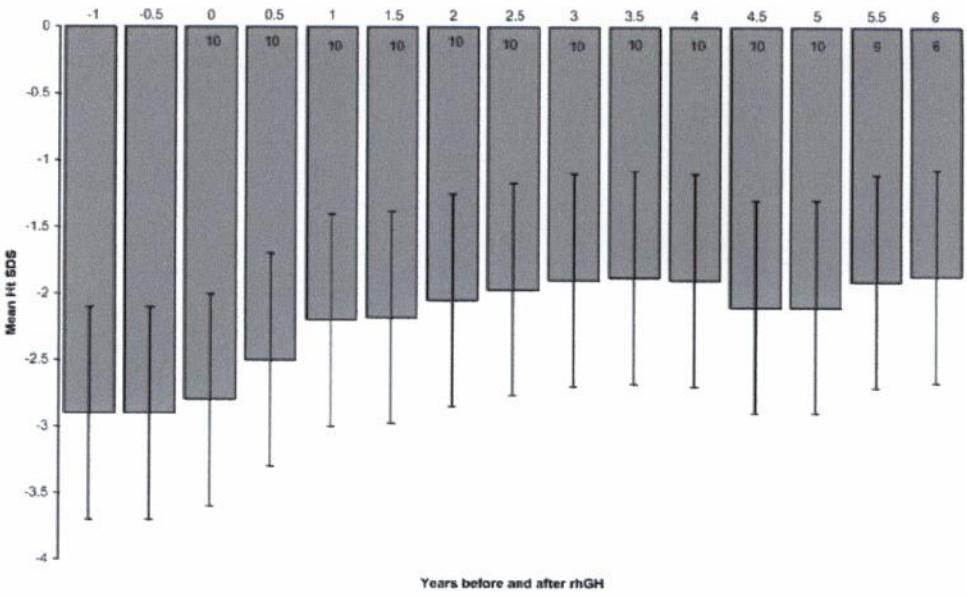

Fig. 1 Ht SDS (SD) at the time of starting rhGH and at six-monthly intervals thereafter in patients who were followed for five years or more of rhGH therapy. The figures at the bases of the columns are the number of patients at different points

RhGH was stopped if transplantation occurred or if the rate of growth declined below that at the start of treatment.

Between the beginning of 1991 and end of 2001, 34 children with conservatively managed CRF or on dialysis were commenced on rhGH treatment. To give an idea of the approximate incidence of rhGH use, there were 204 patients <17 years of age with a glomerular filtration rate (GFR) <40 mL min^{-1}/1.73 m^2 or on dialysis during 2001. The total number of these patients on rhGH was nine (four started during that year), giving an approximate prevalence of 4.4% and incidence of 2% for its use. The low incidence of rhGH use in our centre compared with others may be because of our aggressive use of enteral feeding [9].

Two children were excluded because they received rhGH for less than one year; the remaining 32 (23 boys and 9 girls) were studied. The mean±SD age at the start of rhGH was 8.3±3.7 years; median (range) age 7.7 (1.8–17) years. The mean±SD duration of rhGH therapy was 3.7±2.5 years; median (range) 2.5 (1–12) years.

The etiology of CRF was congenital in 21 children: 15 patients had renal dysplasia, either isolated (6) or in association with posterior urethral valve (5) or solitary kidney (4); three children had autosomal recessive polycystic kidney disease; and three had congenital nephrotic syndrome. Nine children had acquired causes of CRF: two cortical necrosis after cardiac surgery; five focal segmental glomerulosclerosis; one rapidly progressive glomerulonephritis; and one had atypical haemolytic uremic syndrome. Two children had inherited diseases: one cystinosis; and one familial hypomagnesaemia hypercalciuria nephrocalcinosis syndrome.

Twenty-one children were conservatively managed, with a mean (SD) glomerular filtration rate (GFR) of 24±12 mL min^{-1}/1.73 m^2 at the start of the treatment; eleven were on dialysis (five peritoneal dialysis (PD), five haemodialysis (HD)) and one child started on HD and was changed to PD. The dialyzed children were older than conservatively managed children: mean (SD) 10.5 (3.6) vs 7.1 (3.2) years, P=0.008. However there was no significant difference in Ht SDS between the two groups at the start of rhGH. Four children were of pubertal age at the start of rhGH (11 years or older), two from the conservatively managed and two from the dialysis groups.

Twenty nine patients stopped rhGH at a mean±SD age of 12.1±4.0 years because they received a renal transplant. One patient stopped rhGH after 6.5 years (at the age of 13.5 years) because his Ht SDS normalized after 1.5 years of rhGH therapy (from −1.9 to −0.7) and stayed at −0.7 to −0.5 for the following 5 years. The remaining two children were still receiving growth hormone at the end point of the study.

Heights at the time of commencement of rhGH, a year before and at 6-monthly intervals were extracted from the patients' notes. Measurements were continued for 2 (range 1–8) years after rhGH was stopped. Height was measured standing in all but the youngest patient (aged 1.8 year) in whom it was measured lying down. Height was expressed as height standard deviation score (Ht SDS). GFR was calculated using the Schwartz formula.

Results were expressed as mean (SD) or median (range). Paired t-tests were used to determine changes from baseline and analysis of variance (ANOVA) was used to compare the Ht SDS of the same children at different time points. A P value of <0.05 was considered significant.

Results

The mean Ht SDS±SD of all patients 1 year before rhGH treatment was −2.5±1.2, at the start point was −2.5±1.2, −2.3±0.7 at 1 year, −2.1±0.7 at 2 years and −1.7±0.7 at 3 years. The improvement was significant by 2 years post-treatment (P=0.01) and continued to be significant up to 3.5 years (P=0.02). However, after that there was no further improvement in growth: mean Ht SDS at 5 years −2.0±1.2 and at 7 years −2.0±0.8. When we studied patients who were followed for at least 5 years (nine patients) while they were receiving rhGH as a separate group the results were similar (Fig. 1).

When children who were receiving conservative management were studied separately, results were similar to those of all patients (Fig. 2): their mean Ht SDS±SD at the start point was −2.5±1.4, −2.1±0.7 at 1 year, −2.0±0.7 at 2 years and −1.6±0.6 at 3 years. The improvement was significant by 2 years (P=0.01) and continued for 3.5 years (P=0.001). After that there was no change in Ht SDS: −1.9±0.6 at 5 years and −1.9±0.7 after 7 years of therapy. In the dialysed patients Ht SDS at the start point was −2.7±0.5 and improved to −2.3±0.5 at 1 year (P=0.02). However, there was no further change after that: Ht SDS at 2 years −2.2±0.6 and at 3 years

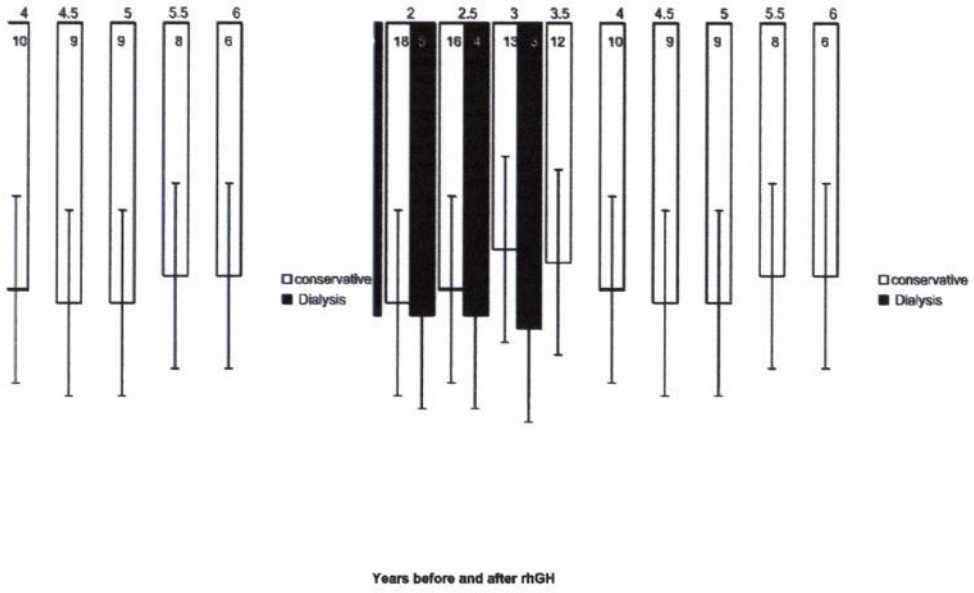

Fig. 2 Ht SDS (SD) at the time of starting rhGH and at six-monthly intervals thereafter in conservatively managed (white columns) and dialysed (black columns) patients. The figures at the bases of the columns are the number of patients at different points

−2.3±0.5 (Fig. 2). When we excluded the two pubertal children from each group, the results were not different. The mean Ht SDS at the start of rhGH for the conservative group was −2.4±1.5, −2.2±0.7 at 1 year, −2.1±0.7 at 2 years and −1.7±0.7 at 3 years. Similarly, in the dialysed patients Ht SDS at the start was −2.8±0.5 and improved to −2.3±0.5 at 1 year

Data were available for 20 patients for more than one year post-transplantation. They received rhGH for a mean of 3.7±2.0 years before transplantation. Ht SDS was: −1.8±0.8 at the stopping of rhGH and transplantation, 1.9±0.7 at 1 year, 2.1±0.6 at 2 years (n=10), −2.2±0.8 at 3 years (n=7), −2.1±0.3 at 4 years (n=4)and −2.1±0.5 at 5 years (n=3). This change in Ht SDS was statistically insignificant. One patient had his rhGH stopped because of normal Ht SDS for 5 years. A slow deterioration of his Ht SDS was observed from −0.6 to −1.6 for the 4 years after cessation of rhGH. RhGH was not re-started because he was post pubertal. Only two patients reached age 18 years. They had discontinued rhGH at the time of transplantation at the age of 13 and 14 years. The Ht SDS were −1.8 and −3.6.

Fasting blood sugars were checked 6-monthly and did not show any derangement in any of our patients and none developed benign intracranial hypertension.

Discussion

Our results are similar to those from previous studies [1, 2, 3] because treatment with rhGH resulted in a significant increase in Ht SDS over the first 3 years in CRF and the first year in dialysis patients but there was no further increase thereafter. The Cochrane review of 10 RCTs showed that rhGH (28 IU m^{-2} $week^{-1}$) resulted in a significant increase in Ht SDS at one year (four trials), and a significant increase in height velocity at six months (two trials) and one year (two trials), but there was no further increase in height indices during the second year of administration [1]. Fine et al. reported in a 24-month study that patients treated with rhGH had a greater growth rate during the first year than during the second year of treatment [2]. However, in a later study they reported that long-term (5 years) treatment of growth-retarded pre-pubertal children with CRF led to a significant and sustained improvement in standardized height from −2.6 at baseline to −0.7 at five years [5]. Similarly, Hokken-Koelega, et al. reported a sustained and significant improvement of Ht SDS compared with baseline values over an 8-year period [10]. These studies differ from ours as we observed that the mean Ht SDS remained at around −2 with no further improvement over 7 years of therapy. In both the American and the Dutch studies, the mean Ht SDS at the start of treatment were comparable with those for our patients (−2.6 and −3 vs −2.5). This variation in long-term growth response between studies could be explained by differences in age, GFR, target height, compliance, length of time with CRF, nutrition, and the pre-treatment growth rate [11].

After discontinuation of rhGH at the time of transplant, we observed no change in Ht SDS. Fine et al. also showed that discontinuation of rhGH at the time of transplantation in 30 patients was associated with absence of post-transplantation "catch up" growth, but patients maintained their Ht SDS (−1.6±1.3 at the time of transplantation, and −1.7±1.2 at last follow-up) [12]. However, continued but slow improvement can occur over a longer period of 10 years [7]. In contrast, NAPRTCS data showed that standardized height (z score) worsened in the majority of paediatric recipients after renal transplantation [13].

In conclusion, rhGH resulted in improvement in growth in children with conservatively managed CRF and on dialysis in the short-term. Discontinuation of rhGH at transplantation resulted in little change in Ht SDS.

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