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ORIGINAL ARTICLE

Obstacles to the prescribing of growth hormone in children with chronic kidney disease

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Abstract Despite its effectiveness, recombinant human growth hormone (rhGH) is under-utilized in short children with chronic kidney disease (CKD). We conducted a multicenter study to explore the obstacles preventing children with CKD from receiving rhGH. We investigated the use of rhGH in 307 children with CKD from seven pediatric nephrology centers. Among the 110 patients who fell below the 5th percentile, 56 (51%) had not received rhGH. The most common reasons given for these children not receiving rhGH were family refusal, secondary hyperparathyroidism, and non-compliance. However, no explanation was apparent for 25% of the short children with CKD. Boys were more likely than girls to receive rhGH (65% vs 31%; P=0.002). Use of rhGH was similar in African Americans and non-Hispanic Whites. Children who had received rhGH achieved a 0.5 increase in height z-score in the first year after the initiation of rhGH therapy. Children who had not received rhGH achieved a 0.03 increase in height z-score during the first year after falling below the 5th percentile (P=0.005 vs the children who had received rhGH). Waiting for insurance company approval led to a significant delay in the initiation of rhGH treatment in 18% of patients. The fact that more than 50% of short children with CKD did not receive rhGH is secondary to multiple factors, many of which may be amenable to intervention efforts.

Keywords Growth hormone · Kidney diseases · Short stature · Secondary hyperparathyroidism · Children

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Introduction

Growth retardation is a well-described complication of chronic kidney disease (CKD) [1]. The etiology is multifactorial and includes inadequate nutrition, metabolic acidosis, renal osteodystrophy, and disturbances in the growth hormone—insulin-like growth factor (IGF)-1 axis [1]. The beneficial effect of recombinant human growth hormone (rhGH) in improving linear growth in children with CKD is well established [2–4]. Moreover, use of rhGH leads to improved adult height in children with CKD [5].

Although short stature in CKD is an approved indication for rhGH therapy, analysis of a large United States database of children with CKD demonstrated that rhGH use is surprisingly low, even in very short children [6]. There is no clear explanation for this low use of rhGH, and we therefore elected to study this issue systematically by identifying obstacles to rhGH use in a large multicenter population of children with CKD.

Methods

This study was a collaborative effort of the Midwest Pediatric Nephrology Consortium and was approved by the Institutional Review Board at each participating institution. This was a retrospective study in which we examined CKD patients with a glomerular filtration rate (GFR) <70 ml/min per 1.73 m^2 body surface area as calculated by the Schwartz formula [7]. Each center examined patients who were seen in the outpatient clinic or the hemodialysis unit over a 3-month period. Enrollment was continued for 3 months or until a target of 50 patients was reached, whichever occurred earlier. We excluded patients if they had received a transplant; had closed epiphyses; had a genetic disorder that would affect growth; or had been diagnosed with CKD within the prior 3 months.

We recorded the following demographic information on each patient: age, gender, race, and ethnicity. We classified patients into four categories: 1. Height always above the 5th percentile and who had never received rhGH; 2. Height always above the 5th percentile and who had received rhGH; 3. Height below the 5th percentile and who had never received rhGH; and 4. Height below the 5th percentile and who had received rhGH. For patients who were below the 5th percentile and had received rhGH, we recorded their height when rhGH had been started and their height 1 year later. For patients who were below the 5th percentile and had never received rhGH, we recorded their height when they were initially below the 5th percentile and their height 1 year later. For children who fell below the 5th percentile and had never received rhGH, we determined if there was a reason why the patient had not been prescribed rhGH and whether rhGH had been discussed prior to the child's falling below the 5th percentile for height. For children who had received rhGH, we determined whether there had been a delay of more than 6 weeks in prescribing rhGH and the reason for this delay.

Groups were compared via the chi square test and paired *t*-test. Statistics were calculated with Sigma Stat 2.03 (SPSS, Inc., Chicago, Illinois, USA). Significance was defined as $P<0.05$.

Results

The records of 307 patients from seven centers were reviewed. There were 193 patients who had always had a height below the 5th percentile and had never received growth hormone (GH); four patients had received GH prior to their falling below the 5th percentile. There were 110 patients who were below the 5th percentile: 54 (49%) had received GH and 56 (51%) had not. Table 1 summarizes demographic and clinical characteristics of the four groups of patients.

There was a diverse range of explanations of why patients with heights below the 5th percentile had never been prescribed rhGH (Table 2). Among children who were below the 5th percentile, boys were more than twice as likely as girls to have received rhGH (65% vs 31%; $P=0.002$). There was no difference in rhGH usage between short African American (43%) and non-Hispanic White (51%; $P=0.46$) children.

A discussion about rhGH therapy prior to the child's falling below the 5th percentile for height only occurred in

Table 1 Demographic and clinical characteristics (*rhGH* recombinant human growth hormone, *SD* standard deviation)

Characteristic	Height <5% and received rhGH ($n=54$)	Height <5% and no rhGH ($n=56$)	Height >5% and received rhGH ($n=4$)	Height >5% and no rhGH ($n=193$)
Age in years (mean ± SD)	8.8±5.5	8.4±5.9	10.5±2.3	11.9±4.8
Female	19%	39%	25%	38%
White (non-Hispanic)	70%	64%	75%	60%
African American	24%	30%	25%	31%
Dialysis	41%	57%	50%	24%

Table 2 Reasons why children below the 5th percentile for height did not receive recombinant human growth hormone

Reason	Number of patients (n=56)
No reason identified	14 (25%)
Family refusal	10 (18%)
Severe hyperparathyroidism	9 (16%)
Non-compliance	5 (9%)
Too young	4 (7%)
Poor nutrition	3 (5%)
Neurologically impaired	3 (5%)
Maintaining growth curve[a]	2 (3%)
Overwhelmed family	2 (3%)
Transplantation scheduled	2 (3%)
Concurrent or recent malignancy	2 (3%)

[a] SD score was below −1.88, but growth velocity was normal

5/27 (18.5%) children who were below the 5th percentile and had never received rhGH. The remaining 29 children who were below the 5th percentile and had never received rhGH were below the 5th percentile when they presented to a pediatric nephrologist.

In children below the 5th percentile for height, there had been a 0.5 increase in height standard deviation score (SDS) during the first year after they had started rhGH therapy. In contrast, children who were below the 5th percentile and had not received rhGH showed a 0.03 increase in height SDS during the first year after falling below the 5th percentile (P=0.005 vs the children who had received rhGH). Of the children who had received rhGH, 76% showed an improvement in height SDS over the next year (vs 43% of the short children who did not receive rhGH; P=0.006).

There was a delay of 6 weeks or longer between prescription of rhGH and the patient's receiving rhGH in 11 of the 56 patients. The explanation for the delay was that the family had not come in for education for one patient (6 week delay) and delays in insurance company approval for ten patients (18% of the rhGH-treated patients, mean delay of 10.6 weeks; SD 4.5 weeks).

Discussion

In this study, 51% of the children with CKD who fell below the 5th percentile did not receive rhGH. In most cases there was a specific reason identified for why the patient was not receiving rhGH. Nevertheless, no reason was identified in 14 of the 56 patients (25%). Owing to the retrospective nature of the study, we can only speculate on why no reason had been identified in the medical record. It is possible that there had been a specific contraindication for rhGH therapy, but is also possible that growth retardation had simply not been addressed. An additional 17 patients (30%) did not receive rhGH because of psychosocial reasons (family refusal, non-adherence, or "overwhelmed family"). Family refusal of rhGH therapy can be due to concerns about daily injections, perceived risk of therapy, and financial concerns. The low use of rhGH in girls suggests that families may balance perceived benefits with perceived burden of therapy. This could be better addressed in a prospective study of patients offered rhGH therapy.

We did not see a significant effect of race on rhGH use. However, boys below the 5th percentile were more than twice as likely as girls to have received rhGH. A more subtle significant negative effect of female gender on growth hormone use was seen in an analysis of the North American Pediatric Renal Transplant Cooperative studies (NAPRTCS) dialysis registry, albeit not in the chronic renal insufficiency or transplant registries [6]. A high percentage of boys in studies of rhGH has been seen in children with growth hormone deficiency [8], idiopathic short stature [9], and survivors of childhood cancer [10]. rhGH appears to be equally effective in girls and boys [5]. Hence, decreased use in girls is most likely due to the perception that short stature is less of an issue for girls.

The use of rhGH in short children in our study was significantly higher than that reported in the NAPRTCS registries. There are a number of potential explanations for the higher use of rhGH in our cohort. One likely explanation is the different methodology. We included all patients who had ever fallen below the 5th percentile for height. This included patients who had received rhGH and then had a height greater than the 5th percentile; such patients are excluded from the NAPRTCS study, leading to an underestimation of rhGH use in short children. In addition, registry data are cross-sectional and may not capture all patients who receive rhGH at some point. The NAPRTCS database is voluntary, and, hence, there may be selection bias or failure to enter data appropriately. We collected data on all patients who had been seen in clinic during a defined time period. We also had more detailed knowledge of the patients, permitting us more accurately to exclude patients with closed epiphysis or syndromes that affect growth. Finally, we collected data from seven centers, while NAPRTCS includes data from over 100 centers. It is possible that there are practice differences in prescribing rhGH in our seven centers when compared to the larger group of pediatric nephrology practices in the USA. It is still notable that our centers, where rhGH therapy is considered to be a highly effective adjunct in the care of short children with CKD, rhGH therapy was only prescribed in 49% of the short children with CKD.

Children who had received rhGH underwent a significant (0.5) increase in height SDS in the first year after

starting rhGH. This is consistent with the efficacy reported in a variety of clinical trials [2–4]. The mean height SDS of the children who had not received rhGH increased minimally (0.03) during the first year after falling below the 5th percentile. This was significantly less than the change in height SDS of the children who had received rhGH. The significance of this comparison may be limited by the non-randomized nature of this observational study, especially since adherence and secondary hyperparathyroidism were commonly cited reasons for not prescribing rhGH in our short children with CKD.

Interestingly, 43% of the children who fell below the 5th percentile had a slight improvement in height SDS during the subsequent year. This suggests that medical intervention might be effective in a number of children with CKD who are below the 5th percentile for height; physicians may be correct in withholding rhGH from this group of patients for some period of time to determine whether renewed attempts to address modifiable causes of growth failure are successful. Once 3–6 months have elapsed, if there has been no improvement in growth velocity after appropriate medical and nutritional interventions, rhGH therapy should be clearly addressed as a treatment option. It would be useful prospectively to study and identify the interventions that are effective in improving growth velocity in children with CKD who are short. This type of study could also help identify parameters that characterize patients who respond well to such interventions.

Many of the short patients had not received rhGH because of accepted contraindications. The most common reason was secondary hyperparathyroidism, which is considered a reason for not initiating or discontinuing rhGH in the practice guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI) [11].

Four children less than 2 years old did not receive rhGH because they were considered “too young”. Many studies of rhGH excluded children less than 2 years old, although rhGH has been used effectively in this patient population [12]. Future studies should determine the appropriate minimum age for which rhGH should be prescribed. Three children did not receive rhGH because they were “neurologically impaired”. There are currently no guidelines on this issue. There is a variety of reasons for withholding rhGH in neurologically impaired patients. It may be viewed as appropriate rationing, given the high cost of rhGH. In addition, the discomfort of daily injections may not be justified in children who are unlikely to derive the psychosocial benefits of improved growth. Finally, it may be more difficult to take care of a taller and heavier neurologically impaired child. Two children were not started on rhGH because of scheduled transplantation; rhGH is generally not prescribed during the first year after transplantation. Two children did not receive rhGH due to a recent or concurrent malignancy. Although the concern that rhGH might increase the risk of leukemia [13] has not been substantiated [14], many clinicians withhold rhGH for patients with a current or recent malignancy. There are no clear guidelines regarding the length of time that rhGH should be withheld following successful treatment of a malignancy.

In many of the patients, rhGH was not given because of a condition that might have been transient (e.g. hyperparathyroidism). It is possible that some patients may receive rhGH in the future with resolution of the transient condition. Conversely, other patients may need to discontinue rhGH because of the development of a contraindication. Other patients had contraindications that were less likely to have been resolved (e.g. severe developmental delay).

A delay of 6 weeks or longer for the prescription of rhGH to the patients actually receiving rhGH occurred in a significant minority of patients. This was due to problems with their obtaining insurance company approval in all cases except one. Future efforts should be directed to eliminating this inappropriate delay for a medication that is medically indicated. Moreover, a future study should examine the role of such difficulties in discouraging physicians from prescribing rhGH to children with CKD.

We did not study patients who had received a kidney transplant. The NAPRTCS study suggests that rhGH use is even lower in this group of patients with CKD [6]. There is a variety of additional issues in prescribing rhGH in this patient population. A similar analysis of rhGH use in this patient population may be useful so that we can better understand the relevant issues.

In conclusion, slightly more than half of short children with CKD are not receiving rhGH therapy. In more than half of these patients, there was no identifiable reason for not using rhGH therapy, or psychosocial issues were identified as the reason for not using this treatment. There is a variety of obstacles to prescribing rhGH in children with CKD. Many of these obstacles may be amenable to intervention, especially, we suspect, the low rate of rhGH use in short girls. Interventions to improve rhGH use in children with chronic renal insufficiency (CRI) could include improved education of families and providers regarding the benefits of therapy. In addition, interventions to alleviate contraindications to rhGH (e.g. hyperparathyroidism) would potentially increase rhGH use.

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