

Chapter 24: Growth and Development

24.1: We recommend measuring growth and development in children (1C):

- at least every 3 months if <3 years old (including head circumference) (*Not Graded*);
- every 6 months in children ≥ 3 years until final adult height. (*Not Graded*)

24.2: We recommend using rhGH 28 IU/m²/week (or 0.05 mg/kg/day) in children with persistent growth failure after kidney transplantation. (1B)

24.3: We suggest minimizing or avoiding corticosteroid use in children who still have growth potential. (2C)

rhGH, recombinant human growth hormone.

Rationale

- CKD and CKD stage 5 can cause growth failure in children before kidney transplantation.
- Despite successful kidney transplantation, growth failure can persist.
- Recombinant human growth hormone (rhGH) is safe and effective in children with growth failure after kidney transplantation.
- Children with growth failure (height <3rd percentile, height target standard deviation score <-2, or height velocity <25% for chronological age) grow faster after kidney transplantation with 28 IU/m²/week of rhGH for 1 year compared to no treatment.
- Long-term steroid use has a negative effect on normal growth in children.
- Steroid minimization/avoidance protocols may be safe and effective in children.

The three major factors that can influence growth following successful kidney transplantation are age at transplantation (prepubertal vs. pubertal), allograft function and use of corticosteroid therapy. The height increment associated with the pubertal growth spurt is suboptimal in patients with CKD (834) and the lack of normal pubertal growth spurt in KTRs contributes to inadequate final adult height (835). Persistent growth failure, despite successful kidney transplantation, led to rhGH use being studied to address concerns regarding efficacy in the presence of corticosteroid immunosuppression, increasing risk of acute rejection and the potential for increasing the already raised incidence of malignancy in an immunosuppressed population.

Randomized controlled trials have shown that rhGH is effective in improving the growth of children with CKD during the first year of administration, with increases in all height indices (836), including children with growth retardation after kidney transplantation. The summary of RCTs, eight of which included children with kidney transplants (836), showed that treatment with rhGH (28 IU/m²/week) resulted in a significant increase in height standard deviation score at 1 year and a significant increase in height velocity at 6 months and 1 year. However, there was no further increase in height indices during the second year of administration, compared to untreated controls. On average, children treated with rhGH had an improvement in height standard deviation score by 0.8, height velocity by 3.8 cm/year and height velocity standard deviation score by 6 above nontreated controls (836). Most of the children in the studies after kidney transplant were on relatively low doses of glucocorticoids, with GFR >20 mL/min/1.73 m² and all were greater than 1 year after transplant with height <3rd percentile, height standard deviation score <-2 or height velocity <25% for chronological age at the time of starting therapy. Overall, there is a moderate level of evidence that rhGH is better than placebo for increasing growth and that 28 IU/m²/week is superior to 14 IU/m²/week (see Evidence Profile and accompanying evidence in Supporting Tables 59–61 at <http://www3.interscience.wiley.com/journal/118499698/toc>). Alternatively, a multicenter placebo-controlled trial showed that a rhGH dose of 0.05 mg/kg/day significantly increased height in children with CKD (837).

Cohort studies in children with CKD have demonstrated that response to rhGH therapy is better in prepubertal than pubertal children (838), and in CKD stages 3 and 4 compared to CKD stage 5 (838). However, in short-term studies, there was no significant difference in the magnitude of rhGH-related growth with either pubertal status (including pediatric KTRs (839,840)) or between CKD stages 3 and 4 compared to CKD stage 5 (836).

Although no RCTs have been published with final adult height as an outcome, published data do provide some indirect support that rhGH improves final adult height in children with CKD, including KTRs. A longitudinal study of children with CKD treated with rhGH and followed until they achieved final adult height indicated that treated children had sustained catch-up growth where untreated matched children had progressive growth failure (838). Improved final height in rhGH-treated children has also been reported from US Transplant Registry data (841). However, it still needs to be determined whether rhGH therapy will

result in an increase in final adult height in children who have received a kidney transplant.

Reported adverse events related to rhGH include asthma, acute rejection, deterioration in kidney function, pittedema, raised fasting glucose and glucose intolerance. However, a meta-analysis found no significant difference between treatment and controls in the change in bone age, kidney function, cholesterol, triglycerides, apolipoproteins and glucose tolerance (836). Additionally, there is no evidence that rhGH acts to advance the pubertal growth spurt.

Persistent growth failure, despite successful kidney transplantation, led to rhGH use being studied to address concerns regarding efficacy in the presence of corticosteroid immunosuppression, increasing risk of acute rejection and the potential for increasing the already raised incidence of malignancy in an immunosuppressed population (842). None of the four RCTs in pediatric KTRs (839,843–845) reported an increase in acute rejection associated with rhGH therapy or an adverse effect of this treatment on graft function. However, two did determine that prior acute rejection history is a risk factor for the development of acute rejection following the initiation of rhGH therapy (844,845). The conclusion drawn from these RCTs was that rhGH is a well-tolerated and effective treatment in growth-retarded KTRs. However, no pharmaceutical company that manufactures rhGH has applied to the FDA or European agencies to extend approval for this treatment to the pediatric KTR population.

Concern about a relationship between rhGH use and the development of renal cell carcinoma in pediatric KTRs receiving growth hormone therapy led researchers to probe databases maintained by the pharmaceutical companies that produce rhGH for evidence of an association (846). Only the International Growth Database collected data on kidney malignancy in KTRs on rhGH. rhGH was not found to be an independent risk factor for the development of renal cell carcinoma (846). Isolated incidents of PTLD have been reported in patients receiving rhGH, but a definitive relationship has not been shown.

When considering rhGH therapy for growth-delayed pediatric KTRs, the health-care provider should inform the patient and family that the benefits to growth need to be balanced with possible adverse events and the difficulty of adhering to a daily subcutaneous injection regimen.

Corticosteroids have been used in pediatric KTRs as maintenance immunosuppressive therapy and as a treatment for acute rejection since the 1960s (847,848). A correlation between a daily corticosteroid dose in excess of 7 mg/m² of body surface area and impaired growth in pediatric

KTRs has been reported (849). Over the years, practitioners have made efforts to reduce steroid use in pediatric KTRs in an effort to avoid the potentially negative impact on growth. In a prospective clinical trial of steroid minimization, researchers studied 35 KTRs at 14–27 months following transplantation, 17 of whom received alternate-day corticosteroid therapy and 18 of whom received daily corticosteroid therapy (850). At 1 year, the mean height standard deviation score was +0.49 in the alternate-day group, compared with –0.12 in the daily-dose group. An analysis of the North American Pediatric Renal Transplant Cooperative Study database also found that short-term improvement in height standard deviation score was associated with alternate-day dosing of corticosteroids (851). No decline in graft function was observed in patients receiving daily vs. alternate-day steroid therapy. However, it is important that, when considering alternate-day dosing as a strategy for steroid minimization, the health-care provider address the potential for increased incidence of nonadherence due to the potential difficulty of this dosing regimen.

In 2001, a pilot study reported the initial positive results of steroid avoidance using anti-IL2 receptor antibody for induction and every 2 weeks for the first 5 months after transplant, in addition to tacrolimus and MMF as maintenance immunosuppression therapy (852). A follow-up report in 2003 indicated a significant improvement in the mean height standard deviation score at 1 year in the corticosteroid-avoidance group when compared with a historical control group who had received corticosteroid treatment daily (853). This led to a prospective multicenter RCT of steroid avoidance where 130 unsensitized primary KTRs 0–21 years of age were randomized to steroid-free vs. steroid-based immunosuppression (2004–2006) with a 3-year follow-up (854). Patients in both arms received tacrolimus and MMF immunosuppression. Preliminary analysis does not reveal an overall significant growth advantage at 1 year in children receiving steroid-free or steroid-based immunosuppression. Longer-term follow-up of current and future RCTs will be important in determining the effect of steroid-free or minimization protocols on growth and graft function in pediatric KTRs.

Research Recommendations

- A RCT is needed to determine whether higher doses of rhGH during puberty improve pubertal growth in children with persistent growth failure after kidney transplantation.
- Further follow-up of ongoing and future studies is needed to evaluate the effect of steroid minimization or avoidance on growth.