

Can recombinant growth hormone effectively treat idiopathic short stature?

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Evidence-based answer

Yes, treatment can increase a child's final height. Injections of recombinant human growth hormone (rGH) at least 3 times a week for 4 to 6 years add 3.7 to 7.5 cm to final height in children between 8 and 16 years of age with idiopathic short stature (strength of recommendation [SOR]: B, 2 small, low-quality, randomized controlled

trials [RCTs]). This population comprises children who are otherwise physically and developmentally normal with a height standard deviation score (SDS) of ≤ -2.0 —comparable to the bottom 2.5% percentile of height—and an adequate response to growth hormone stimulation testing.

Clinical commentary

Do we really want to treat healthy short children?

Parents should understand that children who are treated with rGH will still be short, just less short. A young man with a predicted adult height of 63 inches after 5 years will have an adult height of 65 inches—still short by most measures. Clinical trials of rGH for idiopathic short stature have been small and of poor quality, raising the possibility of unforeseen serious adverse outcomes.

Families need to know that insurance rarely covers treatment, which costs \$100,000. Treating all of the 400,000 children in the United States with idiopathic short stature would cost \$40 billion. Moreover, treating healthy short children with rGH raises questions about the value of height and physical appearance, which are even more difficult to address.

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Children treated with rGH will still be short—just less short

Evidence summary

rGH has been available since 1985. The Food and Drug Administration has approved it for such conditions as growth hormone deficiency, chronic renal insufficiency, Turner syndrome, small size for gestational age, and Prader-Willi syndrome.¹ The use of rGH to treat idiopathic short stature introduces many

clinical, economic, and ethical questions. We have attempted to discern the clinical effectiveness of treatment by focusing on RCTs of rGH therapy while leaving the other substantive issues unexplored.

Final height is arguably the most important outcome measure for the effects of rGH and may be represented as actual height or as a standard deviation score

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rGH treatment is expensive and rarely covered by insurance

(SDS)—actual height minus mean height for age divided by standard deviation of height for age.² This measure standardizes height comparisons for different age groups and is comparable to the percentile values on growth charts.

Growth hormone increases height in girls and boys

A 2003 Cochrane systematic review identified 9 RCTs that evaluated treatment with rGH in children with idiopathic short stature. Only 1 used near final height as its main outcome. Inclusion criteria for this RCT comprised prepubertal girls in the bottom third percentile for height without a known cause.

Of the 40 subjects, only 18 provided consent for randomization. Seven of the 10 girls randomized to the treatment group and 6 of the 8 randomized to the control group completed the study to final height measurement. The average age of the treated girls at the start of therapy was 8.07 years; the average duration of treatment was 6.2 years. All participants reached stage 4 breast development, menarche, and a growth velocity of <2 cm per year in the year preceding final height measurement. Mean final height in the treatment group was 155.3 cm compared to 147.8 cm in the control group—a 7.5-cm difference (95% confidence interval [CI], 3.14-11.86 cm).^{2,3}

A double-blind, placebo-controlled RCT published after the Cochrane review assessed final height in a peripubertal, predominantly male population with non-growth-hormone-deficient short stature.⁴ Inclusion criteria comprised a height SDS <-2.50, but 6 participants with a height SDS between -2.25 and -2.5 were included because of a change in the criteria.⁵ Sixty-eight children were initially randomized. Of the 37 randomized to treatment, 22 were available for final height measurement. The placebo group had a higher dropout rate—only 11 of 31 patients were available for final height measurement. In an attempt to reduce the dropout rate, the final height criteri-

on for discontinuation of injections was changed from <0.5 to <1.5 cm per year. The mean age of the treatment group was 12.5 years at initiation of treatment; average duration of treatment was 4.6 years.

Intent-to-treat analysis of patients who received at least 6 months of treatment with final height assessment revealed a positive treatment effect on height (SDS) of 0.51. This is the equivalent of a 3.7-cm difference in final height for the treatment group compared with the placebo group ($P<.02$; 95% CI, 0.10-0.92 SDS).⁵

Recommendations

The FDA has approved rGH for use in children with height SDS ≤ -2.25 —equivalent to the lowest 1.2% of children. The Lawson-Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee states that rGH therapy should be considered only after accurate diagnosis, careful monitoring of growth velocity, and estimation of final height by a pediatric endocrinologist.^{6,7} ■

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