

**Editor's comments:** This study is important for the data it presents on long-term GH treatment of Noonan syndrome. A recent article by MacFarlane et al (J Clin Endocrinol Metab 2001;86:1953) noted a waning of growth effect after 3 years of GH treatment. It is possible that the optimal dose of GH for Noonan syndrome has not yet been determined and that, as in

the treatment of Turner syndrome, it is a greater dose (based on kilogram of body weight) than usually prescribed for children with idiopathic GH deficiency. Unfortunately, the studies to date do not show an extremely positive response for patients with Noonan syndrome.

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## A Comparison of hGH and IGF-I as Growth-Promoting Agents in Children

Messina et al report the near adult stature of 2 children with isolated GH deficiency type 1A due to partial or complete deletion of the gene complex encoding the human GH gene cluster on chromosome 17q22-q24. In the first patient, only the gene encoding CS-B was retained; she was treated with rhGH for 12 years and achieved a near adult stature greater than her target height (153 cm vs 149 cm). This patient developed only a low titer of rhGH antibodies with low binding capacity. In the second subject, only the GH-N gene was deleted; the patient responded well to the administration of rhGH for 4 years (0.6 to 4.6 years) without development of antibodies to rhGH (height SDS increased from -5.0 to -1.4), but then abruptly developed a high titer of rhGH antibodies with high binding capacity that severely restricted the linear growth response to further rhGH administration (7.3 cm between 4.6 to 8.6 years). This child then received recombinant human insulin-like growth factor 1 (rhIGF-1) (8.6 to 13.9 years; 40 to 120 µg/kg SC twice daily); height increased only 21.2 cm during rhIGF-1 administration and the achieved near/adult height was far less than target height (128.6 cm vs 153.6 cm).

Bacckeljaaw et al describe the linear growth response to rhIGF-1 (80 to 120 µg/kg SC twice daily) in 5 children with loss-of-function mutations in the GH receptor (Laron syndrome) and 3 with deletion of the GH gene and acquired GH insensitivity due to development of high titers of antibodies to rhGH during treatment with this agent. The response to rhIGF-1 was similar in the 2 groups. Overall, the mean pretreatment height SDS was -5.6, (range, -3.4 to -7.0); after 6.5 to 7.4 years of rhIGF-1 administration, mean height SDS was -4.2 (range, -1.5 to -6.6), and only 1 child had achieved a height SDS greater than -2.0. The mean pretreatment growth rate was 4.0 cm/y and increased to 9.3 and 6.2 cm/y during the first 2 years of rhIGF-1 administration but slowed thereafter. Head circumference, weight and fat mass, spleen and kidney size, nasopharyngeal lymphoid tissue, facial soft tissues, and bone mineral density increased during treatment with rhIGF-1.

The authors of both articles concluded that the linear growth response to rhIGF-1 of GH-insensitive subjects is far less than that of GH-deficient patients to rhGH. They attribute the variation in response, in part, to the different effects of GH and IGF-1 on early chondrocyte differentiation and later clonal proliferation, respectively.

Messina MF, et al. Final height in isolated GH deficiency type 1A: effects of 5-year treatment with IGF-I. *Eur J Endocrinol* 2001;144:379-383.

Bacckeljaaw PF, Underwood LE, and the GHIS Collaborative Group. Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: a clinical research center study. *J Clin Endocrinol Metab* 2001;86:1504-1510.

**Editor's comment:** It was disappointing to learn that administration of rhIGF-1 did not restore normal linear growth in children with GH insensitivity. It is now apparent that the circulating concentration of IGF-1 is not as important a determinant of linear growth as is its tissue level. In mice without hepatic IGF-1 production, serum IGF-1 concentrations are low but linear growth is normal, suggesting that it is the local synthesis of IGF-1 that is critical for cartilage proliferation and bone growth. Since serum concentrations of "free" IGF-1 are normal in the animals without hepatic IGF-1 production, they might have accounted for the normal growth of these animals. However, the present studies in humans, in whom it is likely that during treatment "free" IGF-1 values were normal if not high (as IGF-binding protein-3 levels are low in these patients), suggest that it is not circulating but tissue IGF-1 values that are of greater importance for cartilage proliferation and linear growth. It will be of interest to examine the phenotype and response to therapy of the experimental mouse with dual knock-out of the genes encoding the GH receptor and hepatic IGF-1 synthesis.

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Butler AA, LeRoith D. Minireview: tissue-specific versus generalized gene targeting of the *igf1* and *igf1r* genes and their roles in insulin-like growth factor physiology. *Endocrinology* 2001;142:1685-1688.

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