

Treatment, Dosing, and Follow-Up of Children With Primary and Secondary IGFD

In appropriately selected patients, rhIGF-1 is a safe and effective treatment.

BY BARRY B. BERCU, MD

There is increasing evidence for and experience with the role of insulin-like growth factor-1 (IGF-1) therapy in subgroups of poorly growing, short-stature children. Long-term studies demonstrate the safety and efficacy in children with extreme abnormalities of growth hormone (GH) insensitivity.¹

Clinicians are gaining more experience using IGF-1 in children with more subtle forms of growth disturbances. A dosing schedule is important in the decision-making process of the clinician, especially in the weeks after IGF-1 therapy initiation.

GH, IGF-1 CONTRIBUTIONS TO GROWTH

A study done in knockout mice² showed importantly that GH and IGF-1 contribute to 69% of statural growth. GH alone regulates about 14% and IGF-1 about 35% of growth, and 17% of growth is unrelated to either factor.

There are limited data available regarding IGF-1 treatment. Most of what we know comes from studies performed in the 1990s, and these were conducted in children with classic GH insensitivity syndrome (GHIS). Important studies of confirmed or suspected GH receptor defects come from Israel (Laron et al),³ Ecuador (Guevara-Aguirre et al, the only placebo-controlled study),⁴ Europe (Ranke, et al),⁵ and North America (Bacelljauw and Underwood, Chernausek et al).^{6,7}

Clayton et al⁸ evaluated recombinant human (rh)IGF therapy in a large single-site study. They performed only

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arginine stimulation testing (not two tests as is recommended) in a group of 190 children. They found that 46% of children had normal peak GH using a cutoff of >7.6 ng/mL and 24% had IGF-1 standard deviation score (SDS) ≤ -3.0 . The investigators also found that 11% of the population had severe primary insulin-like growth factor deficiency (IGFD). Although this investigation was flawed because one, not two provocative stimuli was used, these observations are still useful. Children with IGFD are patients we know would benefit from rhIGF-1 therapy.

IDEAL DOSING AND RESPONSE

Clinicians are faced with having a limited amount of information to go on when treating these patients, as well as a lack of data on ideal dosing. Chernausek et al⁷ showed that as dose increases—up to a certain point—a better response is seen. Their group treated 76 children with IGF-1 deficiency due to GH insensitivity with rhIGF-1 in doses between 60 and 120 $\mu\text{g}/\text{kg}$ twice daily. Height velocity, skeletal maturation, and adverse events were

measured. They found that height velocity increased from 2.8 cm/yr on average at baseline to 8.0 cm/yr during the first year of treatment ($P < .0001$) and was dose dependent (Figure 1). In their study, height velocities were lower during subsequent years but remained above baseline for up to 8 years.

Cohen et al⁹ also showed that as rhIGF-1 doses increase, there is a better response. In this trial, the investigators gave twice-daily doses of $>100 \mu\text{g}/\text{kg}$ versus $<100 \mu\text{g}/\text{kg}$. Clearly, a better mean height velocity is achieved during the first year with the higher dose (8.3 cm/yr vs 6.3 cm/yr). Although these results are not as good as would be seen by treating a patient with GH deficiency using GH, there is still a significant difference in dosing when using rhIGF-1.

With regard to Chernausek et al's investigation,⁷ a subset of 19 patients of the 71 in the trial received an average dose between 0.10 and 0.12 mg/kg twice daily for the first 2 years of treatment. The investigators found that growth velocity increased to 9.3 cm/yr in the first 6 months, and growth velocity tripled over baseline in the first year. They also found that growth velocity in year 2 more than doubled over baseline and that patients grew an added 14.8 cm (5.8 inch) above pretreatment over 2 years.

Table 1 compares a European⁵ and an American study.⁷ This shows that the rate of growth decreases over time with rhIGF-1 treatment, which is exactly the experience with hGH therapy.

INDICATIONS FOR rhIGF-1 TREATMENT

What are the indications for rhIGF-1 treatment? Not all situations for potential treatment are black and white. Indications include:

- severe primary IGFD: height standard deviation (SD) ≤ -3.0 , normal or elevated GH, IGF-1 SD score -3.0 (US

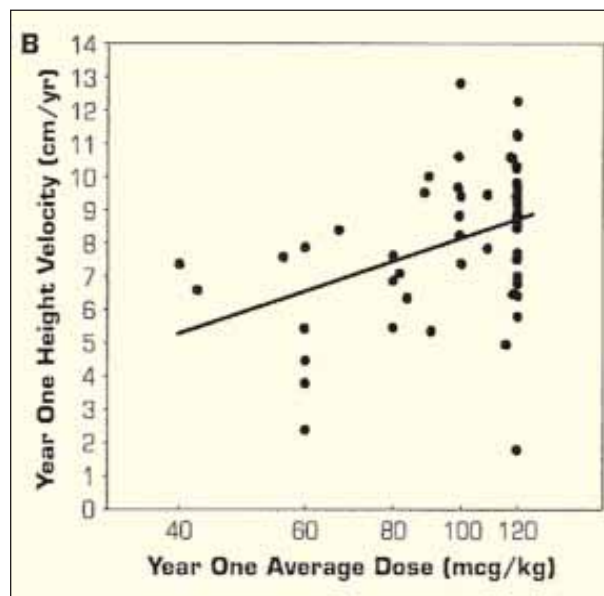


Figure 1. rhIGF-1 dose dependency of first-year growth rate.

Food and Drug Administration [FDA]-approved indication);

- less-severe primary IGFD: height SD < -2.25 , normal GH, IGF-1 SDS < -3.0 ;

- less severe primary IGFD: height SD < -2.25 , normal GH, IGF-1 SDS < -2.0 ;

- GH insensitivity (mutations in GH receptor [GHR] or post-GHR signaling pathway (FDA approved);

- IGF-1 gene defects (FDA approved);

- hGH deletion patients with neutralizing antibodies to GH (FDA approved); and

- non-GHD children who fail on their hGH prescription (a clinical trial should be considered in this last patient population).

Clinical categories of growth failure that may be

TABLE 1. rhIGF-1 TREATMENT IN TWO LONG-TERM STUDIES

| Years on IGF-1 | Ranke et al ⁵ | | Chernausek et al ⁷ | |
|----------------|--------------------------|-------|-------------------------------|---------|
| | (n) | cm/yr | (n) | cm/year |
| 1 | 15 | 8.8 | 59 | 8.0 |
| 2 | 13 | 7.0 | 54 | 5.9 |
| 3 | 12 | 6.8 | 48 | 5.5 |
| 4 | 15 | 5.0 | 39 | 4.8 |
| 5 | 13 | 5.2 | 21 | 4.9 |
| 6 | 6 | 6.3 | 20 | 5.0 |
| 7 | | 16 | | 4.7 |
| 8 | | 14 | | 4.6 |

responsive to rhIGF-1 treatment, include low GH, low IGF-1; low IGF-1, normal or high GH; and inadequate growth on hGH.

RHIGF-1 TREATMENT WHERE NOT INTENDED/CONTRAINDICATIONS

Situations in which IGF-1 treatment should not be used include patients with GH deficiency or insufficiency—we know these patients grow extremely well with hGH therapy. Other situations in which rhIGF-1 is not intended for use include malnutrition, hypothyroidism, patients who are being treated with pharmacologic doses of glucocorticoids (some of these patients are treated with GH), and closed epiphyses. It is important to note that IGF-1 is not a substitute for hGH treatment.

It is important to start patients on low doses and adjust upward over time, although higher doses—at least 100 $\mu\text{g}/\text{kg}$ up to 120 $\mu\text{g}/\text{kg}$ twice a day—are more effective.

The contraindications to rhIGF-1 use include an allergy to the drug or any of its inactive ingredients. The preservative benzyl alcohol can cause neurotoxicity in neonates, and patients can develop sensitivity to the drug. Active or suspected neoplasia is also a contraindication.

Side effects. In the original rhIGF-1 studies, 50% to 85% of patients with Laron syndrome³ experienced side effects, most of which occurred during the first 8 months.^{7,10} Long-term clinical trials^{7,10} with up to 11-year follow-up in 71 patients have shown that 42% had hypoglycemia at least once, 32% had lipohypertrophy at injection site (resolved with rotation), 15% had tonsillar hypertrophy in the first 1 to 2 years (improved over time), and 4% had intracranial hypertension (resolved in two patients without interruption of treatment, a lower dose was successful in the third). No child stopped rhIGF-1 therapy during the trial due to side effects.

Additional transient side effects associated with treatment include arthralgia, myalgia, headache, injection site reactions, and coarsening of facial features. Side effects related to lymphoid tissue growth are hypoacusis, snoring, tonsillar and adenoidal hypertrophy, tympanic membrane tube placement, sleep apnea, adenotonsillectomy, and thymic hypertrophy.

DOSING SCHEME

The initial dosage of rhIGF-1 should start at 40 to 80

$\mu\text{g}/\text{kg}$ twice a day. Doses can be titrated upward in 40- $\mu\text{g}/\text{kg}$ increments at intervals of ≥ 7 days if tolerated. Doses can be increased to a maximum of 120 $\mu\text{g}/\text{kg}$ twice daily, and should be individualized to the patient. Note that dosing $>120 \mu\text{g}/\text{kg}$ twice daily has not been evaluated.

Clinical suggestions for treatment. Use of the somatomedin (IGF-1) generation test is not helpful, except in classic GHIS/Laron syndrome cases (this is more controversial in idiopathic short stature). If the patient has a history of hypoglycemia, provide the family with a glucometer. It is important that treatment is given right after food ingestion. If there is a concern about the child not eating or a history of hypoglycemia, it is acceptable to give IGF-1 after a meal. Practitioners should monitor glucose levels with dosage changes, and consider 2-week intervals to change dosage amounts from 40 to 80 to 120 $\mu\text{g}/\text{kg}$ twice daily. Also, be sure to follow the patient's bone age.

SUMMARY AND IMPLICATIONS

In appropriately selected children, rhIGF-1 is an effective and safe treatment. It is important to start patients on low doses and adjust upward over time, although higher doses are more effective, at least 100 $\mu\text{g}/\text{kg}$ up to 120 $\mu\text{g}/\text{kg}$ twice a day. ■

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