

Anaphylactic Reaction to Recombinant Insulin-like Growth Factor-I

Erika Torjusen, Jose Calderon and Scott A. Rivkees

Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA

ABSTRACT

Mecasermin [rDNA] (Increlex; Tercica, Inc.) is recombinant insulin-like growth factor-I (IGF-I) that has been approved to treat growth failure in children with severe primary IGF-I deficiency. Serious allergic reactions related to Increlex therapy have not been reported. We report a 13 year-old male who developed life-threatening anaphylaxis early in the course of Increlex therapy.

KEY WORDS

IGF-I, allergic reaction, Laron syndrome, growth hormone

INTRODUCTION

Insulin-like growth factor-I (IGF-I) plays an essential role in statural growth and other biological functions^{1,4}. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues, and stimulates the synthesis and secretion of IGF-I. In target tissues, IGF-I acts via specific receptors to exert potent biological effects, including stimulation of cell proliferation and differentiation^{1,3,4}. The epiphyses are an important site of action, where GH promotes the development of mature chondrocytes from stem cells, and local (paracrine/autocrine) production of IGF-I which stimulates clonal expansion of the differentiating chondrocytes contributing to linear bone growth^{1,3,4}.

In rare circumstances, IGF-I production or action is impaired, leading to marked short stature^{2,5-9}. Patients with severe primary IGF-I deficiency typically have normal to high serum GH levels, low height standard deviation (SD) values (< -3 SD), and IGF-I levels below -3 SD³⁻⁹.

Individuals with mutations in the GH receptor do not respond to endogenous GH or rhGH injection, have low circulating levels of IGF-I, and growth failure, a condition referred to as GH receptor deficiency (GHRD) or Laron syndrome. Individuals with GHRD have increases in linear growth when treated with recombinant IGF-I⁵. In addition to individuals with GHRD, it has been suggested that IGF-I deficiency may occur in other individuals with short stature, and a broader role for IGF-I therapy has been proposed, although this remains to be demonstrated^{2,10}.

In 2005, the United States Food and Drug Administration (FDA) granted approval for mecase-
rmin [rDNA origin] injection (Increlex; Tercica, Inc.) for the treatment of growth failure in children with 'severe primary IGF-I deficiency' due to GHRD, post-receptor defects, or GH gene deletion who have developed neutralizing antibodies to GH¹¹⁻¹³. Approval was based on a six-month priority review of data from five clinical trials in 71 pediatric patients showing that mecase-
rmin therapy yielded a significant increase in growth in these conditions of GH insensitivity¹². Serious or allergic adverse events were not reported in this small sample size¹². We now report life-threatening anaphylaxis at the onset of Increlex therapy in a boy with IGF-I deficiency.

PATIENT REPORT

The patient was a male born at term weighing 2.4 kg and measuring 45 cm (both $<3^{\text{rd}}$ percentile) after an uncomplicated pregnancy. Maternal height was 156 cm (10^{th} percentile), and paternal height

Reprint address:

Scott A. Rivkees, M.D.

Yale Child Health Research Center

P.O. 208081

464 Congress Ave.

New Haven, CT 06520, USA

e-mail: Scott.Rivkees@Yale.edu

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165 cm (between 3rd and 10th percentile). From 3 to 11 years of age, growth velocity was 4.1 cm/year (<3rd percentile). At 11 years of age, height z-score was -3.29 and weight z-score was -1.68. Following arginine and clonidine infusion, circulating GH levels rose to a peak of 22 ng/ml; the IGF-I level at the same time was 28 ng/ml (-3.5 SD). At 11.5 years of age, GH therapy was initiated (0.35 mg/kg/week). Bone age at the time was 3 years delayed. On GH, the growth velocity was 3.4 cm/yr and was similar to the pretreatment growth velocity with verified compliance. After one year of GH, the circulating IGF-I level was 31 ng/dl (-3.5 SD) and IGF binding protein-3 (IGFBP-3) level was 0.1 mg/L (normal 0.4 ± 0.2). IGF-I and IGFBP-3 levels were determined at Esoterix Inc. (Calabasas Hills, CA). Because the growth rate did not improve on therapy, GH was discontinued. Primary IGF-I deficiency was diagnosed on the basis of short stature, low IGF-I level, and failure of exogenous GH to increase serum IGF-I level.

After the child had not received GH for 6 months, therapy with Increlex was initiated at the recommended initial dose of 0.04 mg/kg (1.3 mg; 14 U) twice daily by subcutaneous injection. About 6 h after the third dose, circular redness of about 10 cm in diameter developed at the most recent injection site. There were no respiratory symptoms. The redness resolved spontaneously and the patient was given his evening dose, which was well tolerated. Medical personnel were not notified.

About 24 h after the ninth injection (the patient missed the scheduled tenth injection), the patient developed diffuse urticaria, pruritis, respiratory distress, and tongue and pharyngeal itching. He was not taking any other medication and had no known food allergies. He was treated emergently with oxygen, epinephrine, diphenhydramine, and prednisone. He was hospitalized in a pediatric intensive care unit; intubation was not required. Within 24 h, the urticaria and respiratory symptoms resolved and there were no clinical sequelae. Increlex therapy was discontinued.

About one month later, skin testing was performed to test for Increlex sensitivity. Histamine (positive control), histamine diluent (negative control), Increlex and the Increlex diluent were tested. Histamine was administered by skin prick;

other samples were administered by skin prick and intradermal injection.

Following histamine administration, the patient developed a wheal 10 mm in diameter and flare at the skin prick site, as expected. The histamine diluent did not result in detectable skin changes. Following administration of a 1:1 solution of 10 mg/ml of Increlex by skin prick, a cutaneous response was not observed.

When Increlex (0.1 ml of 10 mg/ml solution) was administered intradermally, a 10 x 12 mm wheal and flare developed at the injection site. The intradermal injection triggered systemic responses within 15 min, including pruritis of the lips, sneezing and profuse rhinorrhea, which resolved with oral diphenhydramine.

Injection of Increlex vehicle at a later date did not result in local or systemic responses. Radioallergosorbent (RAST) testing revealed moderate IgE antibody titers against tree nuts, including hazel nuts, Brazil nuts, cashews and pistachios.

Although one cannot exclude the possibility that exposure to other allergens contributed to the severe allergic reaction observed, the presence of a local cutaneous reaction after the third dose, coupled with the development of an acute allergic response following intradermal administration one month after therapy was discontinued, strongly suggests the presence of hypersensitivity to Increlex. This adverse event was formally reported to the manufacturer, who reported this event to the FDA via MedWatch. The patient remains off therapy.

DISCUSSION

Five clinical studies (four open-label and one double-blind, placebo-controlled), with subcutaneous doses of Increlex (60 to 120 µg/kg, twice daily), were conducted in 71 pediatric patients with severe primary IGF-I deficiency¹². Data from these clinical studies were pooled for efficacy and safety analysis that was presented to the FDA¹².

Children were treated for a mean duration of 3.9 years and no patient withdrew from any clinical study because of adverse events. Minor adverse events considered related to Increlex occurred in 5% or more of study participants. Although not related to our patient, mild or moderate hypo-

glycemia was reported by 30 children (42%)¹². Five participants had severe hypoglycemia; four experienced hypoglycemic seizures/loss of consciousness on one or more occasion. Of the patients reporting hypoglycemia, 47% had a history of hypoglycemia prior to treatment. Tonsil hypertrophy was noted in 11 (15%) patients in the first 1-2 years of therapy. Intracranial hypertension occurred in three children¹².

Anti-IGF-I antibodies that did not affect growth response were present in 14 of 23 children with primary IGF-I deficiency treated for 2 years¹². No allergic reactions were observed, nor was anaphylaxis seen. Allergic reactions were not reported among the approximately 80 other patients treated with rhIGF-I¹⁴⁻¹⁶. Importantly, anaphylactic reactions have been reported to insulin, which has some common structural features with IGF-I¹⁷⁻¹⁹.

Our observations indicate the presence of primary allergic sensitivity to Increlex and the development of anaphylaxis shortly after therapy onset in an Increlex-naïve individual. The cause of Increlex sensitivity in this individual is not known. In the GH gene deletion model, the antibodies are inactivating but do not produce an allergic reaction. If he were IGF-I naïve as a result of complete failure of synthesis, one would not have expected levels that were measurable or equally suppressed IGFBP-3 levels. Further studies will be needed to characterize the allergenic component(s) of Increlex in this child.

When considering IGF-I therapy, it is important to consider that IGF-I therapy was tested in only a small number of children before FDA approval. This report highlights the essential need for formal FDA-mandated surveillance of new therapeutics, especially when pre-approval sample sizes are small. This observation emphasizes that physicians need to be cautious and vigilant when new biological therapeutics are used.

REFERENCES

1. Salmon W, Daughaday W. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. *J Lab Clin Med* 1957; 49: 825-836.
2. Rosenbloom AL. Insulin-like growth factor-I (rhIGF-I) therapy of short stature. *J Pediatr Endocrinol Metab* 2008; 21: 301-315.
3. Walenkamp MJ, Wit JM. Genetic disorders in the growth hormone-insulin-like growth factor-I axis. *Horm Res* 2006; 66: 221-230.
4. Laron Z. IGF-I and insulin as growth hormones. *Novartis Found Symp* 2004; 262: 56-77; discussion 77-83, 265-268.
5. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003. *J Clin Endocrinol Metab* 2004; 89: 1031-1044.
6. Rosenbloom AL. Physiology and disorders of the growth hormone receptor (GHR) and GH-GHR signal transduction. *Endocrine* 2000; 12: 107-119.
7. Rosenbloom AL. IGF-I deficiency due to GH receptor deficiency. *Horm Metab Res* 1999; 31: 161-171.
8. Rimoin DL. Hereditary forms of growth hormone deficiency and resistance. *Birth Defects Orig Artic Ser* 1976; 12: 15-29.
9. Rosenbloom AL. The role of recombinant insulin-like growth factor I in the treatment of the short child. *Curr Opin Pediatr* 2007; 19: 458-464.
10. Cohen P. Controversy in clinical endocrinology: problems with reclassification of insulin-like growth factor I production and action disorders. *J Clin Endocrinol Metab* 2006; 91: 4235-4236.
11. Norman P. Mecasermin Tercica. *Curr Opin Investig Drugs* 2006; 7: 371-380.
12. INCRELEX™ (mecasermin [rDNA origin] injection). 2005.
13. Mecasermin rinfabate: insulin-like growth factor-I/insulin-like growth factor binding protein-3, mecasermin rinfabate, rhIGF-I/rhIGFBP-3. *Drugs R D* 2005; 6: 120-127.
14. Guevara-Aguirre J, Rosenbloom AL, Vasconez O, Martinez V, Gargosky SE, Allen L, Rosenfeld RG. Two-year treatment of growth hormone (GH) receptor deficiency with recombinant insulin-like growth factor I in 22 children: comparison of two dosage levels and to GH-treated GH deficiency. *J Clin Endocrinol Metab* 1997; 82: 629-633.
15. Klinger B, Laron Z. Three year IGF-I treatment of children with Laron syndrome. *J Pediatr Endocrinol Metab* 1995; 8: 149-158.
16. Camacho-Hubner C, Underwood LE, Yordam N, Yuksel B, Smith AV, Attie KM, Savage MO. Once daily rhIGF-I/rhIGFBP-3 treatment improves growth velocity in children with severe primary IGF-I deficiency: results of a multicenter clinical trial. 88th Annual Meeting of The Endocrine Society, Boston, MA, 2006; Abst OR 40-1.
17. Kaya A, Gungor K, Karakose S. Severe anaphylactic reaction to human insulin in a diabetic patient. *J Diabetes Complications* 2007; 21: 124-127.
18. Scheer BG, Sitz KV. Suspected insulin anaphylaxis and literature review. *J Ark Med Soc* 2001; 97: 311-313.
19. Gupta SK, Veith FJ, Ascer E, Wengerter KR, Franco C, Amar D, el-Gawet ES, Gupta A. Anaphylactoid re-

actions to protamine: an often lethal complication in insulin-dependent diabetic patients undergoing vascular surgery. *J Vasc Surg* 1989; 9: 342-350.