Final height in a patient with Laron syndrome after long-term therapy with rhIGF-I and short-term therapy with LHRH-analogue and oxandrolone during puberty*

S. Zucchinì, E. Scarano, L. Baldazzi, L. Mazzanti, P. Pirazzoli, and E. Cacciari
Department of Pediatrics, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

ABSTRACT. Objective: To report our experience on long-term treatment with recombinant-human-IGF-I (rhIGF-I) of a female patient with Laron syndrome (mutation G223G in the GH receptor gene), who received short-term treatment (1 yr) with LHRH analogue at the start of puberty and subsequently with oxandrolone. Case report: The patient started IGF-I therapy (dose 40 μg/kg bid for 9 months, 80 μg/kg bid until 13.7 yr of age and 120 μg/kg bid thereafter) when she was 7.6 yr old (height –6 sds), and was treated for 9.4 yr until final height (cm 129.7; –5.5 sds). At first signs of puberty (age 12.7 yr; height 116.3; –5.3 sds), LHRH analogue was started (3.75 mg/28 days) and bone age progressed by 6 months in the 12-month period. Growth velocity decreased in the 6-12th month of combined treatment (0.9 cm/6 months), and treatment was suspended. At age 14.8 (height 124.5; –6.6 sds), oxandrolone was added (0.1 mg/kg/day), but after 12 months (height 128 cm; –5.7 sds) bone age increased from 11.5 to 13.5 yr and the drug was stopped. No side effects occurred during the various treatments. Body segments progressed harmonically: there was a tendency towards improvement in the upper to lower body segment ratio and in cranial growth. Only bililac diameter did not increase during LHRH treatment. During the 9-yr period, body mass index (BMI), subcapular and triceps skinfold centiles did not show any significant variations. Conclusions: Our patient with Laron syndrome after long-term treatment showed a final result below the initial expectations, confirming that IGF-I used with the present schedule is less effective than GH in GH-deficient patients. LHRH analogue therapy at puberty was associated with a slower bone age maturation but with an almost complete arrest of growth. On the contrary, oxandrolone sustained growth but caused an excessive maturation of bone age. Other strategies are necessary to improve final height in these patients.

INTRODUCTION

Although promoting statural growth, treatment with IGF-I in patients affected by GH insensitivity syndrome (GHIS) has so far obtained conflicting results. In fact the two studies providing long-term data in patients with GHIS (1, 2) reported in many cases a catch-up growth that was consistently less than that of patients affected by severe GH deficiency who were treated with appropriate replacement therapy. Possible explanations for this were the lack of direct anabolic actions of GH (3), the short life of IGF-I usually administered twice daily sc without the complex IGFBP3/ALS (4) and a tendency of IGF-I to increase gonadal maturation (5, 6). The study describing the longest period of treatment with rhIGF-I (6.5-7.5 yr) in 8 children affected by GHIS (2), including 5 patients with Laron syndrome and 3 with GH gene deletion, reported height sds improvements ranging in the former from 1.1 to 2.1 sds and in the latter from –1.2 to 4.0 sds. We report our experience of one patient affected by Laron syndrome who underwent long-term treatment (9 yr) till final height with IGF-I, and short-term treatment (1 yr), during the pubertal period, first with

*Presented as an abstract at the 42nd Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), Ljubljana, Slovenia, September 18-21, 2003.

Key-words: GH insensitivity syndrome, GH deficiency, child.

Correspondence: Prof. E. Cacciari, Dipartimento di Pediatría, Ospedale “S. Orsola-Malpighi”, via Massarenti 11, 40138 Bologna, Italy.
E-mail: cacciari@alma.unibo.it
Accepted October 1, 2004.
LHRH analog and subsequently with oxandrolone. The therapy with these two agents, also used in other conditions to improve final height (7-12), was attempted when it was evident that patient height would be less than expected.

CASE REPORT

The patient, of Italian origin and with consanguineous parents, was born at term after an uneventful pregnancy, with a birth weight of 3200 g. A reported height at age 3.9 yr was 77 cm [-5.3 sds according to Tanner’s standards (13)]. She came to our observation for the first time at 7 yr of age, when height was 86.5 cm [-7.3 sds, Italian standards (14)] and weight 11.5 kg [body mass index (BMI) 15.4]. Her phenotype was typical for a severe GH deficiency including, besides severe growth retardation, frontal bossing, midface hypoplasia, high-pitched voice, truncal obesity and small hands and feet. Hormonal findings gave the following results: 1) basal GH levels were 21.5 ng/ml, 2) peak GH response after arginine test was 41.6 ng/ml, 3) she had undetectable IGF-I levels. The molecular analysis of the GH receptor gene (performed by PCR and direct sequencing of the entire coding region) identified the G223G splicing mutation in exon 7 already described in the patients affected by Laron syndrome with severe growth deficiency (15). Both parents resulted heterozygous carriers of this mutation.

Study protocol

We applied to Dr. M.O. Savage for treatment with recombinant human IGF-I (rhIGF-I), and the drug (Igefar, Pharmacia & Upjohn, Stockholm) was available when she was 7.6 yr of age. The treatment protocol was approved by our Ethics Committee and written informed consent was given by the parents. As scheduled, IGF-I was administered sc, in two daily doses (after breakfast and dinner) of 40 μg/kg BW for the first 9 months, 80 μg/kg until age 13.7 yr (considered the pre-pubertal dose) and 120 μg/kg (considered the pubertal dose) until final height (age 16.6 yr). In the last 2 yr of treatment, rhIGF-I was provided through Dr. Underwood by Genentech (San Francisco, USA). Treatment was interrupted for only 2 months when there was the switch between the two providers and she was 14.5 yr of age. At the onset of puberty (breast 1-2) at age 12.7 yr LHRH analogue (Decapeptyl, Ipsen) therapy was added in order to delay the progression of pubertal development at the dose of 3.75 mg/28 days. The combined therapy lasted for 12 months. At 14.8 yr, when the future availability of the rhIGF-I treatment was uncertain, oxandrolone therapy (0.1 mg/day, ie 2.5 mg/day) was added and again the combined therapy lasted 12 months. Approval of the new protocol was obtained from the Ethics Committee and written informed consent was again given by the parents. The patient was seen every 3 months for auxological and laboratory evaluation, for rhIGF-I dose adjustments according to weight and pubertal stage and to record any side effects. A full anthropometric evaluation (head circumference diameter, biacromial and bicipitallac diameters, hand and foot length, triceps and subscapular skinfolds) was performed yearly and at every change of the protocol by the same operator (SE). To evaluate height and growth velocity sds, we used Tanner’s standard (to make our data more comparable with other data published), while for height sds we used also the more recent Italian standards (more accurate for our patient). For the other auxological parameters Prader’s standards (16) were used. Left hand x-ray was performed every 6 months and evaluated by two independent observers with the Greulich and Pyle method.

RESULTS

Figure 1 shows the growth chart of the patient (Tanner’s standards). Although her growth line rose