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Effectiveness and Safety of rhIGF-1 Therapy in Children: The European Increlex® Growth Forum Database Experience

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Key Words

Height · rhIGF-1 therapy · EU IGFD Registry · Short stature · Severe primary insulin-like growth factor-1 deficiency

Abstract

Background/Aims: We report data from the EU Increlex® Growth Forum Database (IGFD) Registry, an ongoing, open-label, observational study monitoring clinical practice use of recombinant human insulin-like growth factor-1 (rhIGF-1) therapy in children. ***Methods:*** Safety and effectiveness data on rhIGF-1 treatment of 195 enrolled children with growth failure were collected from December 2008 to September 2013. ***Results:*** Mean ± SD (95% CI) height velocity during first year of rhIGF-1 treatment was 6.9 ± 2.2 cm/year (6.5; 7.2) (n = 144); in prepubertal patients naïve to treatment, this was 7.3 ± 2.0 cm/year (6.8; 7.7) (n = 81). Female sex, younger age at start of rhIGF-1 therapy, and lower baseline height SDS predicted first-year change in height SDS. The most frequent targeted treatment-emergent adverse events (% patients) were hypoglycemia (17.6%, predictors: young age, diagnosis of Laron syndrome, but not rhIGF-1 dose), lipohypertrophy (10.6%), tonsillar hypertrophy (7.4%), injection site reactions (6.4%), and headache (5.9%). Sixty-one serious adverse events (37 related to rhIGF-1 therapy) were reported in 31 patients (16.5%). ***Conclusion:*** Safety and effectiveness data on use of rhIGF-1 in a 'real-world' setting were similar to those from controlled randomized trials. Severe growth phenotype and early start of rhIGF-1 improved height response and predicted risk of hypoglycemia.

Introduction

Growth disorders resulting from defects in the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis form a continuum, with severe GH deficiency (GHD) at one extreme and severe GH insensitivity at the other [1, 2]. In both conditions, severe IGF-1 deficiency, either sec-

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ondary to GHD or primary in the case of GH insensitivity, causes significant growth retardation as the growth-promoting effects of GH occur mostly via IGF-1 production [3]. Although various genetic defects [4] have been identified with phenotypes varying from mild short stature without dysmorphic features to extreme growth failure associated with Laron syndrome [5–7], there are patients with severe primary IGF-1 deficiency [SPIGFD, defined as height standard deviation score (SDS) less than or equal to –3, IGF-1 <2.5th percentile for age and sex (in the European Union) or IGF-1 SDS less than or equal to –3 (in the United States), and normal or elevated GH secretion [8, 9]] who do not yet have a genetic diagnosis.

Recombinant human (rh)IGF-1 [mecasermin (rDNA origin) injection; Increlex®; Ipsen Pharma, Boulogne Billancourt, France] is approved for the treatment of growth failure in children with SPIGFD. Acquired forms of IGF-1 deficiency, such as those due to malnutrition, hypothyroidism, or chronic treatment with pharmacological doses of anti-inflammatory steroids are excluded from this indication [8, 9].

Clinical trials have demonstrated that children with SPIGFD respond to rhIGF-1 replacement therapy [10, 11]. However, the IGF-1-independent actions of GH on the growth plate cannot be normalized by rhIGF-1 treatment. In addition, the activity of IGF-1 is affected by several IGF-binding proteins (IGFBPs). The lack of GH-dependent IGFBP-3 and acid-labile subunit decreases the serum half-life of IGF-1, which may further contribute to incomplete catch-up growth in children with SPIGFD treated with rhIGF-1.

GH and IGF-1 act in concert to promote linear growth, while their effects on glucose metabolism are opposed. In children with severe GHD as well as those with SPIGFD, the lack of GH glucoregulatory actions may cause spontaneous hypoglycemia [8]. In SPIGFD, this tendency to develop hypoglycemia may be further augmented during rhIGF-1 treatment and it is, therefore, the most common adverse event (AE) [8, 9]. As expected, the risk of hypoglycemia appears to be related to the severity of the IGF-1 deficiency and the lack of GH-dependent IGFBPs [8, 9, 11]. On the other hand, lack of the insulin-like effects of IGF-1 may contribute to the postprandial hyperglycemia observed in SPIGFD, which is corrected by rhIGF-1 therapy [10]. All rhIGF-1 injections should be given simultaneously with a meal, special attention should be paid to the risk of hypoglycemia after exercise, and glucose levels should be monitored in the case of hypoglycemic symptoms. Some of the other reported AEs associated with the mitogenic effects of rhIGF-1 are, to some extent, similar to those of rhGH, and include hypertrophy of lymphoid tissue causing tonsillar enlargement and compromised ventilation of the middle ear. Water retention with soft tissue swelling and, in rare cases, increased intracranial pressure have been reported [10, 11]. Local injection site reactions include lipohypertrophy and redness of the skin [10, 11]. Nonspecific symptoms, such as headache, have also been reported.

The European Medicines Agency (EMA) approved rhIGF-1 (Increlex®) for the treatment of short stature in patients with SPIGFD with a requirement that clinical data should be captured in a registry. The EU Increlex® Growth Forum Database (IGFD) Registry is an ongoing, open-label, observational study that started in December 2008 and which has been initiated in 10 European countries to monitor the safety and effectiveness of rhIGF-1 therapy in children in the clinical practice setting. The EU IGFD Registry also aims to monitor patients after the end of treatment and to the attainment of adult height. The experience of rhIGF-1 treatment in clinical trials with a carefully controlled patient population [10–12] may differ from that in the clinical setting with a heterogeneous patient population; however, registries provide these real-world data, which are currently lacking in this therapy area. The objective of this article is to report safety and effectiveness data (up to 2 years) from children enrolled in the EU IGFD Registry up to September 30, 2013.

Patients and Methods

Patients

Children were eligible for enrollment in the EU IGFD Registry if they were initiating or were currently receiving rhIGF-1 therapy prescribed by a participating qualified practitioner and gave informed consent, if appropriate, in addition to mandatory consent from their parents or legally authorized representative. Children currently participating in either an rhIGF-1 clinical trial or in any clinical trial for growth retardation were excluded from the EU IGFD Registry. Participants or their legal representative could withdraw from the EU IGFD Registry at any time without affecting treatment or normal follow-up of the condition.

Study Procedures

Anonymous data existing in the patients' medical records as part of standard medical care were collected using an electronic Case Report Form. This included sex, birth data, parental heights, height and weight measurements prior to inclusion, previous therapy (including details of growth-promoting therapy with rhGH, rhIGF-1, and/or steroids), data on work-up including medical history, GH secretory status, serum IGF-1 and IGFBP-3 concentrations, genetic testing, and bone age. The baseline clinical examination recorded pubertal stage, auxology (including height, weight, and sitting height), concomitant medication, and starting dose of rhIGF-1.

Baseline was defined as the visit closest to the start of Increlex® treatment. If a patient had previously received growth-promoting treatment, including another preparation of rhIGF-1, baseline still referred to the visit closest to the start of Increlex® therapy.

The number and frequency of follow-up visits for each patient were determined by the investigator's judgment on the basis of clinical need and rhIGF-1 label recommendations. The study defined specific 6-monthly time points up to 60 months for the descriptive analysis. Each visit was allocated to the time point closest to the visit. If several visits occurred within the same time window, only data collected at the visit nearest to the time point were used.

Diagnosis was reported by the treating physician. Data collected during treatment included changes in rhIGF-1 dose and treatment outcomes (e.g. height, weight, pubertal stage), concomitant medications, and serum IGF-1 concentrations.

Safety data included serious adverse events (SAEs), targeted treatment-emergent adverse events (TEAEs, defined as targeted adverse events that have been historically associated with rhIGF-1 treatment or that occurred either frequently whether or not they were considered to be drug-related by the reporting physician; treatment-emergent means occurring while treatment is ongoing) [8], treatment-related nonserious AEs, and clinically significant laboratory abnormalities, occurring from initiation of treatment (including retrospective events on treatment prior to the registration visit) up to completion in the EU IGFD Registry.

The safety data were reviewed on at least an annual basis by an independent data review board composed of pediatric endocrinologists. The EU IGFD Registry was conducted in compliance with independent ethics committees/institutional review boards (except in the UK, where ethical review is not required for this type of registry), informed consent regulations, the Declaration of Helsinki, the International Conference on Harmonization, and the Good Epidemiological Practice Guidelines. In addition, the EU IGFD Registry adhered to all local regulatory requirements including data protection requirements linked to the use of electronic data.

Endpoints

The primary objective of the EU IGFD Registry was to collect long-term safety information on the use of rhIGF-1 therapy for the treatment of children with growth failure. The primary endpoints comprised: description and incidence of any SAE, including new onset and recurrence of neoplasia; incidence of all targeted TEAEs (both treatment related and nontreatment related), i.e. hypoglycemia (suspected and documented: blood glucose level <50 mg/dl or 2.78 mmol/l), lipohypertrophy at the injection site, tonsillar hypertrophy, otitis media, hearing loss, sleep apnea, intracranial hypertension, papilledema, headache, acromegalic facial changes, edema, myalgia, gynecomastia, and cardiomegaly; incidence of any TEAEs considered by the reporting pediatric endocrinologist to be/not to be related to rhIGF-1 therapy, and description and incidence of all clinically significant laboratory abnormalities.

A secondary objective of the EU IGFD Registry was to obtain long-term effectiveness data for rhIGF-1 therapy in children with growth failure. Changes from baseline were calculated for height (cm and SDS), height velocity (cm/year), weight (kg and SDS), body mass index (BMI and SDS), bone age, and pubertal stage according to the Tanner method.

Local protocols and test recommendations were used rather than a central laboratory, and thus there was variation with respect to the assays employed. At each visit the following data were recorded: rhIGF-1 therapy compliance and exposure, serum IGF-1 and IGFBP-3 concentrations, and genetic test results.

Study Populations

This analysis reports results from five populations. Demographic data are presented for the enrolled population, which comprised all patients who were fully informed about the EU IGFD Registry, for whom written informed consent to participate was received, and who complied with the inclusion and exclusion criteria. The effectiveness data are presented for the Registry population, and comprised all enrolled patients who received at least one treatment and completed at least one follow-up visit. The Registry population also included two Registry subpopulations: prepubertal patients (Tanner stage 1 of genital development for boys and breast development for girls) at first rhIGF-1 intake who were also naïve to growth-promoting treatment (treatment-naïve/prepubertal population), and patients who had previously received growth-promoting treatment or who were pubertal (Tanner stage 2 or above of genital or breast development for boys or girls, respectively; previously treated/pubertal population). Safety data are reported for the safety population, comprising patients who received at least one dose of rhIGF-1 and who attended at least one follow-up visit or for whom there were poststudy treatment safety data. Safety data were also assessed in the treatment-naïve/prepubertal versus the previously treated/pubertal subpopulations within the safety population.

Entering puberty during the first year of rhIGF-1 treatment could potentially affect the first-year change in height SDS and, therefore, a subpopulation of treatment-naïve/prepubertal children that continued to be prepubertal at the first-year visit was also assessed.

Data Analysis

For France and southern European countries, height and weight SDS were calculated using Sempé reference means and SD values [13], with reference values dependent on sex and age. As discrete values for age are contained within the Sempé curve, mean and SD for ages between two reference ages were imputed using linear interpolation. The SDS was calculated as:

$$\mathrm{SDS} = \frac{\left(\mathrm{value} - \mathrm{mean}_{\mathrm{interpolated}}\right)}{\mathrm{SD}_{\mathrm{interpolated}}}.$$

For France and southern European countries, BMI SDS was calculated using the French National Plan for Nutrition and Health (PNNS) reference means and SD values.

For the UK, Belgium, Germany, Sweden, and Poland, height, weight, and BMI SDS were calculated using UK reference values. The reference values, which are dependent on age and sex, were selected at the closest age below that of the patient. The SDS in each case was calculated as:

$$\mathrm{SDS} = \frac{\left(\left(\mathrm{value} / \mathrm{M}\right)^{\mathrm{L}} - 1\right)}{\mathrm{LS}},$$

where L is the reference power, M is the mean, and S is the coefficient of variation.

Annualized year 1 height velocities (cm/year) were computed using baseline and year 1 (days 275–457) height values.

Statistical Analyses

Results are presented as descriptive analyses: mean and SD or median and two-sided 95% CI of the median, maximum-minimum range, or 25th and 75th percentiles. For categorical variables the 95% CIs are provided to show whether population CIs overlap and thereby lack significant difference.

A linear regression analysis was performed to identify predictive factors for first-year height velocity and first-year change in height SDS in treatment-naïve/prepubertal patients. Sex, parental height (cm), height (SDS) at baseline, BMI at baseline, IGF-1 (ng/ml) status at baseline, treatment dose [μg/kg twice daily (BID)] at rhIGF-1 initiation, and age (years) at treatment initiation were entered into the model as covariates. For univariate and multivariate regression analyses, two-sided 95% CIs and p values are reported. The significance level for multivariate analyses was fixed at 5%.

In patients followed for at least 1 year, annualized height velocity (cm/year) was compared between those with an average year 1 dose ≤100 μg/kg BID and those who received an average year 1 dose >100 μg/kg BID using a t test.

The proportion of children with at least one hypoglycemic event was explored using a logistic regression model. In the case of multiple events, the first event was considered. Covariates included age (years), sex, pubertal stage (prepubertal stage vs. pubertal stage) at baseline, dose (μg/kg BID) at the time of hypoglycemia [average dose (μg/kg BID) during first year of treatment for those without hypoglycemia], history of hypoglycemia, previous rhGH therapy, and Laron syndrome.

Results

Patient Characteristics

From the 10 European participating countries a total of 195 patients (Austria 6, Belgium 1, France 35, Germany 73, Italy 23, Poland 9, United Kingdom 22, Spain 20, Sweden 6, The Netherlands 0) were enrolled in the EU IGFD Registry as of September 30, 2013, representing approximately 60% of the estimated population receiving rhIGF-1 treatment for short stature in elective countries (based on the number of patients treated with rhIGF-1 according to the label [14]). At 12, 24, 36, 48, and 60 months, the number of patients who had attended visits were 151, 104, 66, 25, and 5, respectively. This corresponds to a mean ± SD treatment duration of 832 ± 491 days (median 798 days), which is equivalent to a total of 433 patient-years on treatment (n = 190, data missing for 5 patients). In the treatment-naïve/prepubertal and the previously treated/pubertal groups, treatment durations were 835 ± 457 days or 249 patient-years (n = 109; data missing from 1 patient) and 827 ± 538 days or 178 patient-years (n = 79; data missing from 3 patients), respectively.

Baseline characteristics for enrolled patients, treatment-naïve/prepubertal patients (n = 110), and previously treated/pubertal patients (n = 82) are shown in table 1. Baseline characteristics between the treatment-naïve/prepubertal and previously treated/pubertal populations were not significantly different except for mean age at first rhIGF-1 intake, which was 3.5 years earlier in the treatment-naïve/prepubertal group, and mean height and mean IGF-1 concentration, which were both lower in the treatment-naïve/prepubertal patients (table 1). Of those diagnosed with SPIGFD, 7 treatment-naïve/prepubertal patients and 9 previously treated/pubertal patients had a pretreatment height SDS greater than –3 according to the investigator. Calculated baseline height SDS greater than –3 were found in 48 treatment-naïve/prepubertal patients and in 23 previously treated/pubertal patients. In addition, 1 patient with data not available regarding pubertal status and previous treatment was diagnosed with SPIGFD with a height SDS greater than –3.

Of the total number of patients enrolled in the EU IGFD Registry, 165 (84.6%) had SPIGFD as their primary diagnosis according to the reporting physician. Of these patients, 28 were reported to have Laron syndrome (GH receptor deletion or mutation genetically confirmed in 26 patients). Diagnoses other than SPIGFD were reported in 24 of these patients, including small for gestational age (n = 4), Noonan syndrome (n = 3), bone dysplasia (n = 3), and diabetes mellitus (n = 2). The primary diagnosis in the remaining 30 patients who were not diagnosed with SPIGFD included: primary IGF-1 deficiency (n = 17, 56.7%), GH gene deletion with anti-GH antibodies (n = 2, 6.7%), small for gestational age (n = 5, 16.7%), and bone dysplasia, diabetes mellitus, and Russell-Silver syndrome (n = 1, 3.3%, for each). Other primary diagnoses accounted for 10 patients (33.3%). The investigator was able to record more than one primary diagnosis for each patient.

Previous growth-promoting therapy had been given to 65 patients (33.3%): 52 of these (80.0%) had previously received rhGH treatment and 21 (32.3%) had received rhIGF-1. Both rhGH and rhIGF-1 had been given to 9 patients (13.8%), either simultaneously or over different periods of time, and 5 patients (7.7%) had received steroid treatment (androgen in n = 1 and systemic glucocorticoids in n = 4) prior to inclusion in the EU IGFD Registry. Of those on previous rhGH therapy (n = 47), the median (95% CI) maximum rhGH dose was 0.05 mg/kg/day (0.04; 0.06) and the median duration of treatment was 2.2 years (range: 0.2–12). Thus, in the majority of these patients, including 10 patients who were born small for gestational age, a dose higher than that currently recommended by the EMA (0.025–0.035 mg/kg/day for GHD and a maximum dose of 0.067 mg/kg/day for small for gestational age) had been used (with poor response).

Table 1. Baseline characteristics of all enrolled patients and subgroups of the Registry population: treatment-naïve/prepubertal patients and previously treated/pubertal patients

Characteristic	All enrolled patients (n = 195)			Treatment-naïve/prepubertal patients (n = 110)			Previously treated/pubertal patients (n = 82)		
	n[a]	mean ± SD [95% CI]	median (25th, 75th percentile)	n[a]	mean ± SD [95% CI]	median (25th, 75th percentile)	n[a]	mean ± SD [95% CI]	median (25th, 75th percentile)
Female, n	195	67 (34.4%) [28.1; 41.3]	N/A	110	44 (40.0%) [31.3; 49.3]		82	23 (28.0%) [19.5; 38.6]	N/A
Age at first injection, years	195	10.1±4.0 [9.5; 10.7]	10.6 (6.8, 13.2)	110	8.5±3.5 [7.8; 9.2]	8.3 (5.8, 11.2)	82	12.0±3.6 [11.2; 12.8]	12.4 (10.2, 14.5)
Height, cm	183	116.5±20.0 [113.6; 119.4]	118.5 (100.6, 133.5)	105	110.2±19.3 [106.5; 113.9]	110.1 (96.0, 125.5)	75	124.2±17.8 [120.1; 128.2]	126.6 (112.0, 137.1)
Height SDS	183	−3.5±1.3 [−3.7; −3.3]	−3.2 (−4.4, −2.6)	105	−3.4±1.3 [−3.6; −3.1]	−3.0 (−3.9, −2.5)	75	−3.8±1.3 [−4.1; −3.4]	−3.3 (−4.6, −2.7)
Weight SDS	182	−3.1±1.4 [−3.3; −2.9]	−3.0 (−3.8, −2.1)	104	−3.1±1.2 [−3.4; −2.9]	−3.1 (−3.7, −2.4)	75	−3.2±1.6 [−3.5; −2.8]	−2.9 (−4.1, −2.1)
BMI SDS	167	−0.7±1.5 [−1.0; −0.5]	−0.8 (−1.6, 0.0)	95	−0.8±1.3 [−1.1; −0.5]	−0.8 (−1.7, −0.1)	69	−0.7±1.7 [−1.1; −0.2]	−0.7 (−1.5, 0.0)
Bone age, years	38	8.5±3.5 [7.4; 9.6]	8.5 (5.5, 11.5)	22	7.4±3.0 [6.1; 8.7]	8.0 (5.0, 10.0)	15	9.7±3.7 [7.7; 11.8]	11.5 (6.8, 12.4)
Mother's height, cm[b]	178	157.2±8.2 [156.0; 158.4]	158.0 (151.9, 163.0)	101	157.7±7.3 [156.3; 159.2]	158.0 (153.6, 162.0)	74	157.0±9.2 [154.7; 159.0]	157.5 (151.0, 164.0)
Father's height, cm[b]	176	172.1±7.9 [170.9; 173.2]	172.0 (167.9, 178.0)	100	172.6±8.1 [171.0; 174.2]	173.0 (168.0, 178.0)	73	171.3±7.8 [169.5; 173.1]	172 (166.0, 177.0)
IGF-1, ng/ml[c]	167	120.7±121.6 [102.1; 139.3]	85.0 (44.0, 142.0)	90	91.8±71.0 [76.9; 106.6]	73.5 (38.9, 123.0)	74	157.3±157.7 [120.7; 193.8]	101.9 (54.0, 204.0)
GH test: stimulated, ng/ml	133	27.8±38.7 [21.1; 34.4]	16.8 (11.3, 29.0)	78	24.4±25.0 [18.7; 30.0]	15.6 (11.0, 26.1)	52	32.9±53.6 [18.0; 47.8]	18.1 (11.4, 39.0)
Height velocity, cm/year	109	4.8±1.7 [4.5; 5.1]	4.7 (3.9, 5.6)	57	5.0±1.9 [4.5; 5.5]	5.1 (4.0, 6.2)	51	4.6±1.5 [4.2; 5.0]	4.4 (3.8, 5.4)
Primary diagnosis: SPIGFD[d], n	195	165 (84.6%) [78.9; 89.0]	N/A	110	99 (90.0%) [83.0; 94.3]	N/A	82	63 (76.8%) [66.6; 84.6]	N/A
History of hypoglycemia, n	195	11 (5.6%)	N/A	110	4 (3.6%)	N/A	85	7 (8.2%)	N/A
Prior growth-promoting therapy, n	195	65 (33.3%)[e] [27.1; 40.2]	N/A		N/A	N/A		N/A	N/A

[a] Number of patients for whom data are available; pubertal status/previously treatment status was unknown for 3 patients. [b] Height SDS of 0 corresponds to 174.5 cm in males and 163.2 cm in females aged 18 years in the Sempé reference; height SDS of 0 corresponds to 177.1 cm in males and 163.6 cm in females aged 18 years in the UK 1990 reference. [c] Wash-out period prior to rhIGF-1 therapy start not required in patients with prior growth-promoting treatment. [d] Including Laron syndrome. [e] rhGH in 52 (80.0%) and rhIGF-1 in 21 (32.3%). N/A = Not applicable.

rhIGF-1 Dosing

The recommended starting dose of rhIGF-1 is 40 μg/kg BID by subcutaneous injection [8]. If no significant treatment-related AEs occur for at least 1 week, the dose may be raised in increments of 40 μg/kg to the maximum dose of 120 μg/kg BID. Within the Registry population, the median (95% CI) rhIGF-1 starting dose was 40.0 μg/kg BID (40.0; 40.0) (n = 186). Although dose escalation was slower than recommended, a median dose of 116.0 μg/kg BID (100.0; 120.0) was achieved at 12 months (n = 169). The recommended maximum dose was reached in most patients by 18 months (median 120.0 μg/kg BID,

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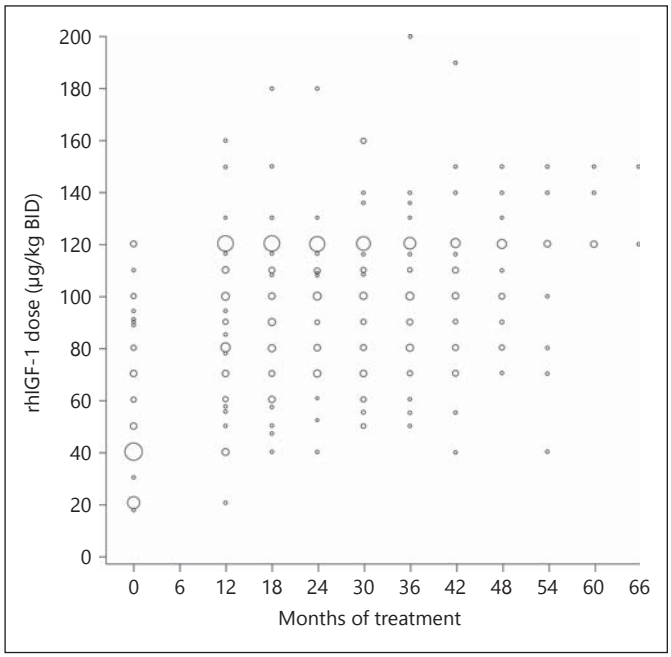

Fig. 1. rhIGF-1 therapy dose received during treatment period (155 patients with at least one follow-up visit). The size of the bubbles is proportional to the number of patients receiving the dose.

95% CI: 116.0; 120.0). Nevertheless, it is evident from figure 1 that some patients did not reach the maximum dose of 120 µg/kg BID. Dosing was similar in the treatment-naïve/prepubertal population (median values at baseline, month 12, and month 18 were 40, 110, and 120 µg/kg BID, respectively). In the previously treated/pubertal population, the maximum recommended dose of 120 µg/kg BID was already achieved by month 12.

Effect of rhIGF-1 Therapy on Height, Weight, and BMI

Mean ± SD (95% CI) annualized height velocity during the first year of rhIGF-1 treatment in the Registry patients was 6.9 ± 2.2 cm/year (6.5; 7.2) (n = 144). First-year height velocity in the treatment-naïve/prepubertal patients [7.3 ± 2.0 cm/year (6.8; 7.7); n = 81] tended to be higher than in previously treated/pubertal patients [6.3 ± 2.4 cm/year (5.6; 6.9); n = 60]. Three patients did not have complete information on puberty/previous treatment. Changes in height and height SDS are provided in table 2.

In treatment-naïve/prepubertal patients who continued to be prepubertal at 1 year, the mean ± SD first year change in height SDS was 0.5 ± 0.4 (n = 67) as compared with 0.4 ± 0.4 (n = 81) in all the treatment-naïve/prepubertal patients (table 2).

Interestingly, treatment-naïve/prepubertal patients with Laron syndrome who were younger [mean age ± SD (95% CI): 6.4 ± 3.3 years (4.3; 8.6); n = 12] and shorter [mean height SDS ± SD (95% CI): –5.9 ± 1.7 (–7.0; –4.9); n = 11] at first rhIGF-1 intake than the treatment-naïve/prepubertal population [8.5 ± 3.5 years (7.8; 9.2), n = 110 and –3.4 ± 1.3 (–3.6; –3.1), n = 105, respectively] had a mean ± SD (95% CI) first-year gain in height SDS of 0.7 ± 0.5 (0.3; 1.1) (n = 8) compared with 0.4 ± 0.4 (0.3; 0.5) (table 2) in the treatment-naïve/prepubertal patients.

Height velocity at year 1 in treatment-naïve/prepubertal patients with a mean rhIGF-1 dose ≤100 µg/kg BID and >100 µg/kg BID was 7.2 and 7.4 cm/year, respectively. In previously treated/pubertal patients with a mean rhIGF-1 dose ≤100 µg/kg BID or >100 µg/kg BID, the first-year height velocity was 6.0 and 6.5 cm/year, respectively. These differences were not significantly different in either group. Predictors of a higher first-year change in height SDS in the treatment-naïve/prepubertal population (multivariate analysis) included: younger age at rhIGF-1 initiation [estimate; 95% CI by 1 unit increment: –0.04 (–0.06; –0.02); $p < 0.001$], female sex [0.18 (0.02; 0.33); p = 0.026], and lower height SDS at baseline [by 1 unit increment: –0.06 (–0.12; –0.00); p = 0.041]. The only predictor (multivariate analysis) of a higher first-year height velocity in the treatment-naïve/prepubertal population was younger age at rhIGF-1 initiation [estimate; 95% CI by 1 unit increment: –0.13 (–0.25; –0.01); $p < 0.033$]. No predictors for first-year change in height SDS were identified in the previously treated/pubertal population.

The mean ± SD height response during the first 2 years of treatment in the Registry population and in the treatment-naïve/prepubertal and previously treated/pubertal subpopulations were 13.0 ± 3.7 cm (n = 98), 13.6 ± 3.2 cm (n = 60), and 11.9 ± 4.2 cm (n = 38), respectively (table 2).

The association between height velocity during the first and the second year of treatment demonstrated that treatment-naïve/prepubertal patients and previously treated/pubertal patients with a good first-year response had better linear growth during the second year than those with a poorer first-year response (R = 0.39, p = 0.004 and R = 0.44, p = 0.006, respectively; fig. 2).

Weight and weight SDS increased more than height and tended to move BMI SDS slightly closer to zero in the Registry group as well as in both subpopulations (table 2). A greater increase in height but smaller gain in BMI was seen in the treatment-naïve/prepubertal population compared with the previously treated/pubertal group.

Table 2. Height, weight, and BMI in the Registry population, treatment-naïve/prepubertal patients, and previously treated or pubertal patients

Height[a]	n[b]	Mean ± SD, cm	Mean SDS ± SD	Change from baseline		
				n[a]	mean ± SD, cm	mean SDS ± SD
Registry population						
Baseline	176	116.6±20.0	−3.5±1.3	–	–	–
Year 1	151	123.7±20.0	−3.2±1.4	144	6.9±2.3	0.3±0.4
Year 2	104	128.3±20.5	−3.1±1.6	98	13.0±3.7	0.6±0.6
Treatment-naïve/prepubertal patients						
Baseline	102	110.5±19.2	−3.4±1.3	–	–	–
Year 1	87	119.6±19.6	−2.9±1.3	81	7.3±2.0	0.4±0.4
Year 2	62	123.8±20.0	−2.9±1.5	60	13.6±3.2	0.7±0.6
Previously treated/pubertal patients						
Baseline	71	124.2±17.9	−3.7±1.3	–	–	–
Year 1	63	128.9±18.9	−3.6±1.5	60	6.3±2.5	0.2±0.4
Year 2	42	134.8±19.7	−3.6±1.7	38	11.9±4.2	0.5±0.7
Weight	**n[a]**	**Mean ± SD, kg**	**Mean SDS ± SD**	**Change from baseline**		
				n[a]	mean ± SD, kg	mean SDS ± SD
Registry population						
Baseline	174	23.0±9.6	−3.1±1.4	–	–	–
Year 1	151	27.2±10.9	−2.5±1.5	142	3.9±2.3	0.5±0.6
Year 2	104	30.9±12.7	−2.6±1.8	96	7.6±4.1	0.7±0.8
Treatment-naïve/prepubertal patients						
Baseline	101	19.3±6.8	−3.1±1.2	–	–	–
Year 1	87	23.8±8.8	−2.5±1.5	80	3.4±1.7	0.5±0.6
Year 2	62	26.5±10.0	−2.3±1.9	59	6.9±3.7	0.8±0.8
Previously treated/pubertal patients						
Baseline	70	27.5±10.5	−3.1±1.6	–	–	–
Year 1	63	31.7±11.7	−2.6±1.5	59	4.6±2.7	0.4±0.6
Year 2	42	37.5±13.5	−2.3±1.7	37	8.8±4.6	0.6±0.7
BMI	**n[a]**	**Mean ± SD, kg/m^2**	**Mean SDS ± SD**	**Change from baseline**		
				n[a]	mean ± SD, kg/m^2	mean SDS ± SD
Registry population						
Baseline	161	16.3±3.1	−0.7±1.5	–	–	–
Year 1	151	17.1±3.3	−0.4±1.4	130	0.7±1.1	0.3±0.7
Year 2	104	18.1±4.2	−0.2±1.6	89	1.2±1.5	0.2±0.7
Treatment-naïve/prepubertal patients						
Baseline	92	15.4±2.0	−0.8±1.3	–	–	–
Year 1	87	16.1±2.4	−0.6±1.4	72	0.5±1.0	0.2±0.7
Year 2	62	16.8±3.3	−0.5±1.6	54	1.0±1.4	0.2±0.7
Previously treated/pubertal patients						
Baseline	66	17.3±3.9	−0.6±1.72	–	–	–
Year 1	63	18.4±3.9	−0.1±1.44	55	1.0±1.1	0.4±0.6
Year 2	42	20.0±4.8	0.2±1.6	35	1.6±1.7	0.2±0.6

[a] Median (Q1; Q3) of the time between the baseline and the year 1 height measurements: registry population: 365 (342; 403) days; treatment-naïve/prepubertal population: 365 (351; 394) days. [b] Number of patients for whom data are available at each time point; pubertal status/previously treatment status was unknown for 3 patients.

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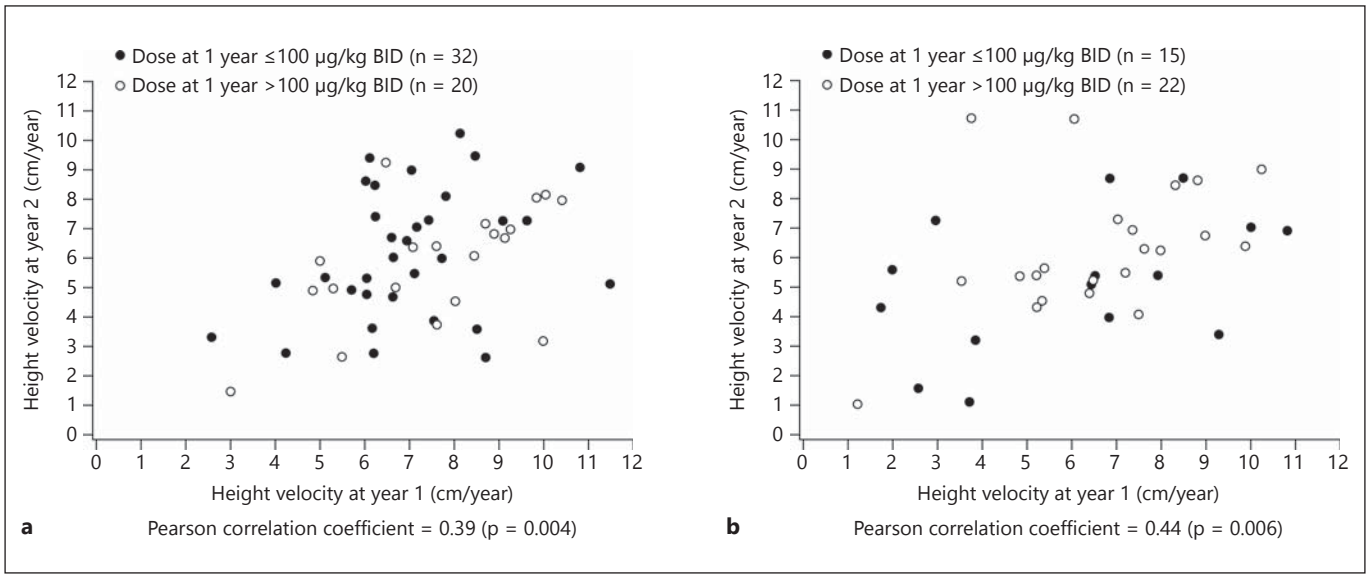

Fig. 2. Height velocity at year 2 according to height velocity at year 1 in treatment-naïve/prepubertal children (**a**) and those who had previously received growth-promoting therapy or who were pubertal (**b**).

Safety Profile of rhIGF-1 Therapy

Safety follow-up data were available for 188 patients; 52.7% of patients (n = 99) reported one or more TEAEs (349 events). Most TEAEs (56.2% of events) were considered to be related to treatment. One or more targeted TEAEs was reported in 39.4% of patients (n = 74), with 84.5% of events being considered to be related to treatment.

Targeted TEAEs

The most frequent targeted TEAE was hypoglycemia [59 events in 33 patients (17.6%)], including 26 events verified by blood glucose measurements (<2.78 mmol/l). Eight of the hypoglycemic events in 5 patients were considered to be serious. Four of 33 patients reporting hypoglycemia had a history of hypoglycemia. Univariate linear regression analysis did not identify a higher rhIGF-1 dose to be associated with hypoglycemia [odds ratio (OR) = 1.0; 95% CI: 1.0; 1.0]. In the Registry population, 18 of 73 patients (24.7%; 95% CI: 16.2; 35.6) with a dose at year 1 of ≤100 µg/kg BID had at least one episode of hypoglycemia compared with 14 of 96 patients with a dose at year 1 of >100 µg/kg BID (14.6%, 95% CI: 8.9; 23.0). Univariate linear regression analysis demonstrated that hypoglycemia was related to age at the start of treatment [OR = 0.9 (95% CI: 0.8; 1.0) by 1-year increment] and to a diagnosis of Laron syndrome (OR = 4.3; 95% CI: 1.8; 10.6). There was no association between the rhIGF-1 dose at the time of hypoglycemia and the age at first administration of rhIGF-1 therapy.

The occurrence of other targeted TEAEs is shown in figure 3. In the treatment-naïve/prepubertal patients (n = 107), 92 targeted TEAEs were reported in 41 patients (38.3%) compared with 63 targeted TEAEs in 33 pubertal/previously treated patients (n = 78; 42.3%).

Clinically Significant Laboratory Abnormalities

In 29 patients (15.4%), a total of 103 nonserious, clinically significant laboratory abnormalities were reported, of which 15 in 12 patients (6.4%) were considered to be related to treatment. The latter included liver and thyroid test abnormalities, decreases in hemoglobin and bilirubin, and out-of-reference ranges for GH–IGF-1-axis components. A median (95% CI) serum IGF-1 concentration of 317 µg/l (281; 386) was reported at 12 months (n = 99), related to an increase from baseline of 237 µg/l [198; 309 (n = 92)]. These levels were not defined relative to time of rhIGF-1 injection. The IGF-1 levels obtained after 1 year did not clearly change with increasing treatment duration. In patients who had previously received growth-promoting therapy, median (95% CI) serum IGF-1 concentration increased from 124 µg/l (76; 161) (n = 51) at baseline to 303 µg/l (221; 455) (n = 27) at year 1, and 369 µg/l (203; 433) (n = 22) at year 2. In contrast, serum IGFBP-3 concentration at baseline [median 1,900 µg/l (95% CI: 1,539; 2,200),

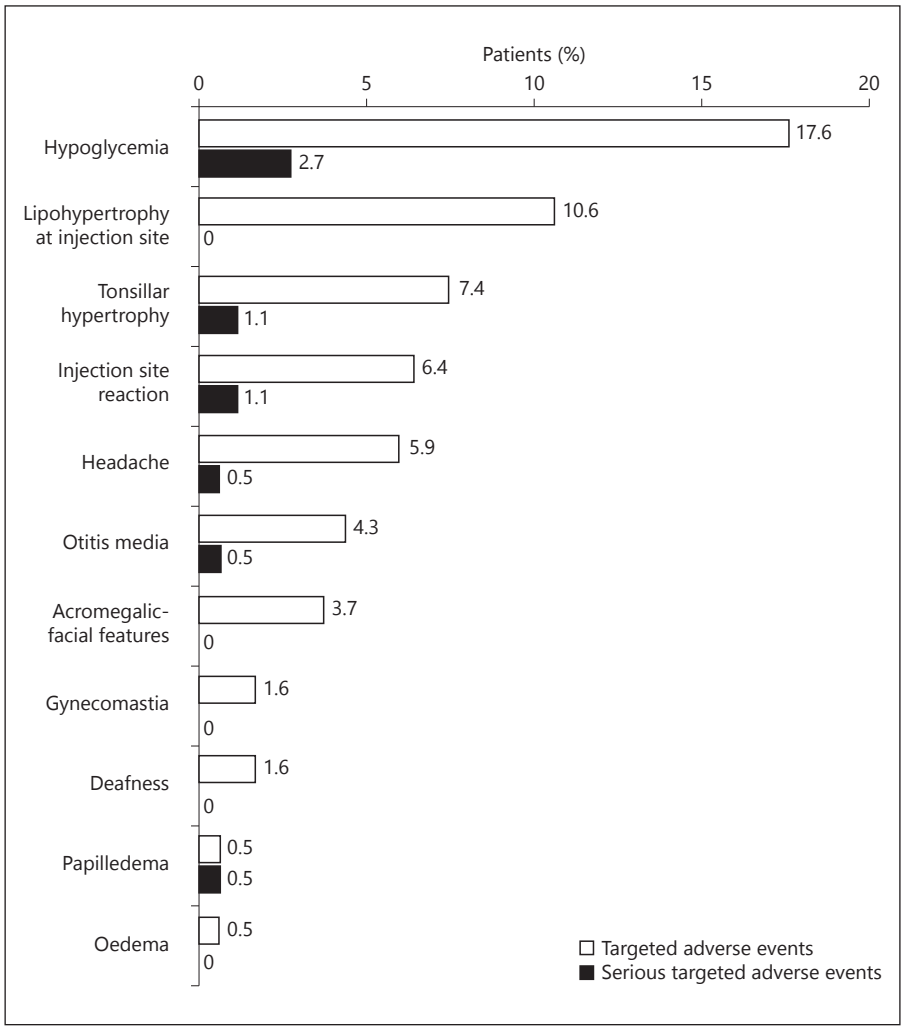

Fig. 3. Total and serious targeted TEAEs (safety population). Hearing impairment was coded as deafness.

n = 120] was unchanged at 1 year [median 1,480 μg/l (95% CI: 1,180; 2,000), n = 68; median change 55 μg/l (–136; 140), n = 52], with no clear changes with increasing treatment duration.

Serious Adverse Events

A total of 61 SAEs were reported in 31 patients (16.5%). Of these, 37 SAEs were considered to be related to rhIGF-1 therapy (table 3). In the majority of patients, there was no change in treatment, or treatment was interrupted or delayed. Four patients who were naïve to treatment terminated therapy due to recurrence of injection site reactions with redness and swelling, thyroid nodule (biopsy was not performed and data to support a malignancy are lacking), angioedema (Quincke's edema), or splenic infarction in a patient with a medical history including splenomegaly, hypersplenism, and autoimmune lymphoproliferative syndrome. Treatment was terminated due to acromegalic facial changes (hypertrophy of the nose; table 3) in 1 patient who had previously received growth-promoting therapy. Premalignant disease (myelodysplasia) leading to death was observed in 1 patient, and after review by the sponsor this SAE was considered to be related to treatment. A further 23 SAEs in 17 patients (9.0%) were reported, but were not considered to be related to rhIGF-1 therapy by the treating physician. The number of SAEs was 35 in the treatment-naïve/prepubertal patients (15.9% of subpopulation) and 26 in the pubertal/previously treated patients (17.9%).

Other Treatment-Related, Nonserious TEAEs

There were 29 other treatment-related, nonserious TEAEs in 22 patients (11.7%), including endocrine disorders (hypothyroidism, secondary hypothyroidism), hair

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Table 3. Serious TEAEs considered to be treatment related (safety population, n = 188)

AE	Events, n	Patients presenting at least one event, n (%)	Hospitalized[a]		Change in treatment[a]			
			yes	no	no change	dose changed	delayed/ interrupted	terminated
All	37	24 (12.8)[b]						
Blood and lymphatic system disorders	3	1 (0.5)	1	0	0	0	0	1
Hypersplenism[c]	1	1 (0.5)	1	0	0	0	0	1
Splenic infarction[c]	1	1 (0.5)	1	0	0	0	0	1
Splenomegaly[c]	1	1 (0.5)	1	0	0	0	0	1
Congenital, familial, and genetic disorders	2	1 (0.5)	1	0	1	0	0	0
Hydrocele	2	1 (0.5)	1	0	1	0	0	0
Eye disorders	1	1 (0.5)	1	0	0	0	1	0
Papilledema	1	1 (0.5)	1	0	0	0	1	0
Gastrointestinal disorders	2	1 (0.5)	1	0	0	0	1	0
Volvulus	1	1 (0.5)	1	0	0	0	1	0
Volvulus of small bowel	1	1 (0.5)	1	0	0	0	1	0
General disorders and administration site conditions	4	3 (1.6)	1	2	0	0	1	2
Hypertrophy[d]	1	1 (0.5)	0	1	0	0	0	1
Injection site induration	1	1 (0.5)	1	0	0	0	1	0
Injection site pruritus	1	1 (0.5)	1	0	0	0	1	0
Injection site reaction	1	1 (0.5)	0	1	0	0	0	1
Immune system disorders	1	1 (0.5)	1	0	0	0	1	0
Hypersensitivity	1	1 (0.5)	1	0	0	0	1	0
Infections and infestations	1	1 (0.5)	1	0	0	0	1	0
Toxoplasmosis	1	1 (0.5)	1	0	0	0	1	0
Metabolism and nutrition disorders	8	5 (2.7)	4	1	0	2	4	0
Hypoglycemia	8	5 (2.7)	4	1	0	2	4	0
Musculoskeletal and connective tissue disorders	1	1 (0.5)	1	0	1	0	0	0
Arthralgia	1	1 (0.5)	1	0	1	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2	2 (1.1)	1	1	0	0	0	2
Thyroid neoplasm[e]	1	1 (0.5)	0	1	0	0	0	1
Myelodysplastic syndrome[f]	1	1 (0.5)	1	0	0	0	0	1
Nervous system disorders	3	3 (1.6)	2	1	0	0	3	1
Headache[g]	1	1 (0.5)	0	1	0	0	1	0
Hypoglycemic unconsciousness[h]	2	2 (1.1)	2	0	0	0	1	1
Paresthesia	1	1 (0.5)	1	0	0	0	1	0
Reproductive system and breast disorders	2	2 (1.1)	1	1	1	0	1	0
Ovarian enlargement[g]	1	1 (0.5)	0	1	0	0	1	0
Testicular torsion	1	1 (0.5)	1	0	1	0	0	0
Respiratory, thoracic, and mediastinal disorders	5	4 (2.1)	4	0	3	0	1	0
Adenoidal hypertrophy	3	3 (1.6)	3	0	3	0	0	0
Tonsillar hypertrophy	2	2 (1.1)	2	0	1	0	1	0
Skin and subcutaneous tissue disorders	2	2 (1.1)	1	1	0	0	1	1
Angiedema	1	1 (0.5)	0	1	0	0	0	1
Dermatitis allergic	1	1 (0.5)	1	0	0	0	1	0

[a] Number of patients. [b] Includes 1 case of myelodysplastic syndrome reported as unrelated to treatment by physician but considered related to treatment by sponsor (see footnote f). [c] Splenomegaly and hypersplenism were preexisting and part of the patient's autoimmune lymphoproliferative syndrome; type 1 diabetes mellitus complicated by retinopathy and hypothyroidism was also preexisting. [d] Soft tissue (nose) hypertrophy. [e] Negative for tumor markers; underwent sonography every 3 months with no progress; biopsy/pathological evaluation not considered necessary. [f] Premalignant disease (myelodysplasia) leading to death, reported as unrelated to treatment by physician but considered related to treatment by sponsor. [g] Considered serious, as associated with significant disability/incapacity. [h] One patient with hypoglycemic unconsciousness, reported as unrelated to treatment by physician but considered related to treatment by sponsor.

disorders (alopecia, dandruff, hair texture abnormal, hair growth abnormal), and clinical signs (abdominal pain, asthenia, hepatosplenomegaly, central obesity, bone pain, melanocytic nevus, dysplastic nevus, dyspnea and snoring, allergic pruritus, weight increase, dizziness, adenoidal hypertrophy, arthralgia).

Completion or Termination of rhIGF-1 Therapy

Ten of 195 patients (5.1%) completed the study because they were reported to have reached their adult or near-adult height. SPIGFD was listed as the primary diagnosis in 8 patients, of which 4 had Laron syndrome (GHR gene defect). Primary diagnoses in the 2 remaining patients were GH gene defects associated with the development of anti-rhGH antibodies, and PIGFD with an IGF gene defect. These patients achieved a mean adult height SDS ± SD of –3.4 ± 2.0 (range: 0.46 to –6.5 SDS) with a mean ± SD treatment duration of 1,078.3 ± 327.2 days. rhIGF-1 therapy was ended at a median age (range) of 17.3 years (16.2–21.1). Of the 4 patients who achieved adult height SDS of less than –3.4, all were pubertal before starting rhIGF-1 treatment and 3 had a severe phenotype at baseline with a height SDS of less than –5.0.

Treatment was terminated in 57 of 195 patients (29.2%); termination was due to an AE in 6 patients (3.1%; for SAEs, see above and table 3), noncompliance with therapy in 3 patients (1.5%), lack of effectiveness in 16 patients (8.2%), and patient/parent or physician choice in 18 patients (9.2%). A further 14 patients (7.2%) terminated treatment for other reasons.

Discussion

This is the first published report of the safety and effectiveness of rhIGF-1 treatment of short stature in clinical practice across 10 European countries, representing 60% of the treated European population [14]. The first-year height velocity was 7.3 cm/year in treatment-naïve, prepubertal children and 7.4 cm/year in those treated with an rhIGF-1 dose of >100 μg/kg BID, approaching the maximum recommended dose of 120 μg/kg BID in the Increlex® product label. Among the treatment-naïve/prepubertal patients, those with Laron syndrome were younger and shorter at baseline, and had a better gain in height SDS after 1 year of treatment. This is in line with our observation that younger age and lower height SDS at baseline predicted a better response in treatment-naïve/prepubertal patients. Furthermore, it was evident from the baseline data that not all of the treatment-naïve/prepubertal patients reported to have SPIGFD fulfilled the diagnostic criteria in the EU: height less than –3 SDS, IGF-1 <2.5th percentile (approx. less than –2 SDS), and normal GH secretion.

Hypoglycemia was the most frequently reported AE in the EU IGFD Registry. Univariate analysis showed that a diagnosis of Laron syndrome or young age at baseline tended to increase the risk of hypoglycemia, which supports the existence of a predestined risk of hypoglycemia in SPIGFD [10]. Eight hypoglycemic events in 5 patients were reported as SAEs, which strongly emphasizes that the recommendations in the Increlex® product label to administer treatment shortly before or after a meal or snack should be strictly followed. There was an accumulation of SAEs in a few patients with complicated comorbidity in addition to their short stature, and this is clearly a group in which caution should be taken and the indication for treatment reconsidered.

Patient diagnoses were reported by the treating physicians. Reporting in similar registries of rhGH therapy has revealed that when applying strict diagnostic criteria many patients will have their reported diagnosis changed [15]. We were unable to confirm a primary diagnosis of SPIGFD in patients enrolled in the EU IGFD Registry. Central laboratory analysis was not used in the EU IGFD Registry and many IGF-1 assays in clinical practice do not define the 2.5th percentile (or –2 SDS). In previously treated/pubertal patients, baseline IGF-1 could be confounded by ongoing rhGH or rhIGF-1 treatment. However, this was not the case in treatment-naïve/prepubertal patients, in whom the high median IGF-1 at baseline suggested that less than the reported 90% of patients fulfilled the IGF-1 requirement. In the treatment-naïve/prepubertal patients, we evaluated the compliance with the definition of SPIGFD with respect to height SDS of less than –3; in those reported to have SPIGFD, only 7 patients had a baseline SDS greater than –3 SDS according to the investigator, but 48 patients had a calculated baseline SDS greater than –3 SDS. In the previously treated/pubertal patients with SPIGFD, 9 had a reported baseline height SDS greater than –3 SDS while 23 had a calculated baseline height SDS greater than –3 SDS. In some of these patients, previous rhIGF-1 treatment may have improved height before enrolment in the EU IGFD registry. Fewer than 25% of the treatment-naïve/prepubertal patients had a stimulated GH maximum below 10 ng/ml (25th percentile: 11.0 ng/ml). A high stimulated GH maximum and/or elevated spontaneous baseline GH are characteristics of GH insensitivity [16] while the diagnostic criteria for SPIGFD is 'normal or elevated GH secretion'. The lack

of consensus on how to define the cutoff between GHD and normal makes it hard to establish which GH status should define SPIGFD.

Given that registries rely on the collection of preexisting clinical data, we were unable to confirm the diagnosis of SPIGFD and thereby look for height responses in patients other than those in the Laron subgroup. Therefore, we used multiple regression analysis to identify height response markers as well as assess the effectiveness of rhIGF-1 therapy in children who were naïve to treatment and prepubertal at baseline. We identified young age and low height SDS as positive predictors of first-year change in height SDS. Our finding suggests that treatment should be started early in life and should be restricted to children who fulfill the diagnostic criteria of SPIGFD. Optimal height response to rhGH treatment in children with approved indications is also achieved in those who are young and short at the start of treatment [15, 16]. However, a mean age of 8.5 years (as per the treatment-naïve/prepubertal children at start of rhIGF-1 treatment) is a common starting age for rhGH therapy (reviewed in [16]). Another positive predictor of first-year gain in height SDS was female sex. We are unsure about how this result should be interpreted. The rhIGF-1 dose was not identified as a predictor of first-year height velocity or gain in height SDS, and thus does not confirm the importance of dose in previous trials of rhIGF-1 therapy in less severe primary IGF-1 deficiency patients [12].

The mean first-year height velocity of 7.4 cm in the treatment-naïve/prepubertal patients treated with an rhIGF-1 dose >100 μg/kg BID was comparable with responses reported in rhIGF-1 trials in SPIGFD [10, 11] and in the recent rhIGF-1 trial in less severe IGF-1 deficiency defined as height and IGF-1 SDS less than –2 and GH maximum >7 ng/ml [12]. These height responses are slightly less than the response to rhGH in idiopathic GHD but significantly less than those in severe GHD [15, 17]. IGF-1-independent growth-promoting effects of GH, as well as the IGF-1-supporting actions of GH-dependent IGFBP-3 and ALS, are thought to be important for this difference. In a study of long-term follow-up to adult or near-adult height of patients with SPIGFD who received rhIGF-1 treatment, an increase in BMI and body fat measured by dual-energy X-ray absorptiometry was reported [18]. We found that BMI increased, approaching 0 SDS during the first year of treatment. The risk of future obesity resulting from slightly faster catch-up of weight versus height cannot be ruled out. However, accumulation of fat appears to be a late event, as supported by the early loss of adiposity on dual-energy X-ray absorptiometry when re-starting rhIGF-1 therapy reported in 2 patients with Laron syndrome [19].

We did not observe any new safety signals in the EU IGFD Registry compared with those previously reported in children treated with rhIGF-1. The targeted TEAEs reported in the EU IGFD Registry were less frequent compared with previous rhIGF-1 treatment trials of SPIGFD [10, 11] but of a similar frequency to those in less severe primary IGF-1 deficiency [12]. Hypoglycemia, suspected or verified by determination of blood glucose, was the most common targeted TEAE, confirming previous observations. Younger age at the time of first rhIGF-1 dose and a diagnosis of Laron syndrome increased the risk of hypoglycemia, whereas rhIGF-1 dose and time from start of rhIGF-1 treatment did not affect the risk. This is the first published risk assessment of hypoglycemia that has been undertaken in clinical practice for rhIGF-1-treated children with short stature. In this assessment, we cannot exclude the possibility that failure to identify the effect of dose is influenced by failure to complete dose escalation to the recommended effective dose of 120 μg/kg/day BID in patients with an expected risk of hypoglycemia. However, the specific risk of hypoglycemia associated with dose was not found in the trial by Midyett et al. [12].

The EU IGFD Registry database has included patients since December 2008. Only 10 patients have reached adult or near-adult height with a mean of less than –3.4 SDS. In patients with SPIGFD, similar adult or near-adult height was reported by Backeljauw et al. [18]. In the EU IGFD Registry, of the 4 patients with a final or near adult height less than –3.4 SDS, 3 had an adult height SDS less than –5.0. Two patients with genetically verified defects in the GH receptor [19] and with an adult height expectancy of 120–130 cm, reached adult heights of 156.5 and 160.6 cm, respectively, which are extremely valuable results. The finding that almost one third of the patients terminated treatment before reaching adult height may seem worrying, even though this was due to AEs in only a few patients. The number of patients reporting poor compliance as a reason for stopping treatment was low considering the twice-daily injection schedule, and poor compliance may have contributed to the poor response observed in some patients.

In conclusion, data from patients in the real-world clinical setting of the EU IGFD Registry are similar to those from previous clinical trials, and therefore confirm the efficacy and safety profiles of rhIGF-1 therapy, previously reported in those trials.

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