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Real world data on rhIGF-1 therapy in children with severe primary IGF-I deficiency – The European experience☆

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ABSTRACT

The Growth Hormone – Insulin-like Growh Factor - axis promotes linear growth in children and adolescents and accounts for approximately 1/3 of adult height. In Primary IGF-I deficiency (PIGFD) insensitivity to the actions of GH results in short stature. The most severe phenotype in children with genetic defects in the GH receptor gene is known as Laron Syndrome with height SDS of −6 to −12 in childhood and an adult height of 120–130 cm. Treatment with recombinant human (rh) IGF-1 is approved to promote linear growth in children with severe PIGFD and the EMA approval required that data on children on therapy and up to 5 years post-treatment is collected in the Global Increlex Growth Forum Database (IGFD) registry.

In this review, the findings in five publications on rhIGF-1 therapy in children with SPIGFD based on data from the Global IGFD registry are discussed and compared with previous publications on cohorts of patients with severe PIGFD including children with Laron Syndrome. The registry started inclusion of patients in 2008 from 10 European countries (EU IGFD Registry) and have continued collecting data from eight European countries and the US since 2021 (Global IGFD registry). At data cut-off (03 April 2025), there were 346 patients in the registry database including patients with a large variation of phenotypes from Laron Syndrome to a less severe phenotype. The findings include real-world data on effectiveness assessing short- and long-term height gain as well as near adult height, pubertal development and growth dynamics and safety assessing hypoglycemic events, which is the most frequent targeted adverse event. Real-world data from the Global IGFD registry confirms previous data on rhIGF-1 therapy and demonstrates that short and long-term height improves in a majority of children with SPIGFD with similar height improvements compared to children with Laron Syndrome. The registry data points to baseline characteristics including age at treatment initiation that predicts response to therapy. Hypoglycemia is the most common adverse event and hypoglycemia prior to start of therapy or a diagnosis of Laron Syndrome increases the risk. However, very few events over a course of therapy are reported on an individual basis.

1. Introduction

Children with severe growth stunting, starting during the first year of life, due to insensitivity to the actions of Growth Hormone (GH), were first described by Zvi Laron et al. in Israeli patients [1,2]. Other sporadic cases were reported from the Middle East and Europe in the following years. Initially, it was thought that the condition was caused by a biological inactive GH molecule, however, in 1984 Laron and his team [3] demonstrated that patients with "Laron type short stature" had a receptor incapable of binding GH. The associated syndrome characterized by proportional short stature and dysmorphic facial features including a hypoplastic middle face, frontal bossing, relative adiposity, and hypoglycemia in the newborn and continuing in childhood, and associated with late puberty, was named Laron syndrome following the first meeting on GH insensitivity in 1993 [4]. Later on, populations of Laron syndrome patients from two provinces of Ecuador [5,6] and many sporadic cases from other countries were also reported [7]. Simultaneously with the characterization of the GH receptor gene in 1989, more

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than one genetic defect in the GH receptor gene were described in some of the original Israeli patients demonstrating genotype variability in this small cohort of patients with identical phenotype. Several different genetic variants in the GHR have been associated with the Laron syndrome phenotype, in most cases affecting the extracellular GH binding domain of the receptor and resulting in severe-to-extreme short stature progressing with age (−4 to −10 height standard deviation score [SDS]). Other genes downstream the GHR leading to a similar growth phenotype have also been described in more detail [8]. Less severe insensitivity to GH may contribute to short stature in children resulting in Insulin-like Growth Factor (IGF) —I deficiency as well as impaired expression of IGF Binding Protein (IGFBP)-3 and Acid Labile Subunit (ALS). These deficiencies affect postnatal growth toward the end of the first year of life, when gene expression of these proteins becomes GH dependent [9]. The term Primary IGF-I deficiency (PIGFD) in contrast to Secondary IGF-I deficiency resulting from GH deficiency, has been suggested for these conditions [10].

Following the report from Laron et al. [11], several clinical trials in Europe, USA and other countries were conducted exploring the effectiveness and safety of recombinant human IGF-1 (rhIGF-1) therapy in GH insensitive children with severe short stature. These clinical trials were made possible by pharmaceutical companies in the US, EU and Japan who developed rhIGF-1 in the late 1980s and beginning of the 1990s. Most of the trials defined GH insensitivity considering its biochemical characteristics including low IGF—I, elevated GH secretion and in some studies a poor IGF-I generation after a few days treatment with sc. injections of recombinant human GH (rhGH). After the conclusion of clinical trials in the USA, the FDA approved the use of rhIGF-1 for the treatment of SPIGFD defined by short stature with height SDS less than −3, IGF-I SDS less than −3 and normal or elevated GH. The FDA indication also included treatment of insensitivity to GH due to the production of GH neutralizing antibodies (which occurs in children with GH1 gene defect treated with rhGH). Two years later, in 2007, EMA approved the use of rhIGF-1 for the treatment of SPIGFD defined as a height SDS less than −3, IGF-I less than the 2.5th percentile (corresponding to approximately −2 SDS) and normal or elevated GH, with a requirement to collect safety and efficiency data in a registry in 10 EU countries. This review focuses on real-world observational data that have been published based on result from the European Increlex® Growth Forum Database (Eu-IGFD) Registry, and its recent expansion including centers in the US, known as the Global Increlex® Growth Forum Database.

The global IGFD registry will allow the future collection of data on Quality of Life and may provide more insights into the psychosocial aspects of short stature in SPIGFD children and their families. This will be important in addition to understanding genetic aspects, diagnosis and treatment, [12] given that the impact of SPIGFD on the lives of patients and their families remains poorly understood [13]. SPIFGD represents a significant burden for patients, their parents and caregivers, and leads to difficulties related to mobility, access to education, finding the right size clothes and creating an ergonomic environment for their adult life [14]. Furthermore, short stature impacts the way in which children are perceived by peers and adults including diminished intellectual ability and intelligence for which there is no evidence [15] Although, treatment is effective, as will be evident from this review, it is not accessible to children with SPIGFD and their families in large areas of the world due to a lack of approval from health entities and economic barriers related to the very high cost of the drug [16]. Even in parts of the world where treatment is accessible, the lack of information, the waiting time to be referred to a pediatric endocrinologist to be diagnosed and start treatment, are sources of anxiety and despair for the families.

2. The Global IGFD database observational study

2.1. Study design

The Global IGFD Registry is an ongoing, descriptive, multicenter, prospective, open ended, non-interventional, post authorization surveillance registry (NCT00903110) [17,18]. The registry has collected real-world clinical data on the use of rhIGF-1 from ten European countries since December 2008 (The EU IGFD Registry) and has continued collecting data from eight European countries and the US since 2021. Our latest publication from the registry is based on data from the Global IGFD Registry, however, so far, data from the US does not include patients who have reached NAH. One of the objectives of the Global IGFD Registry is to follow patients for at least 5 years after the end of rhIGF-1 treatment. Children are eligible to participate in the global registry if they are starting treatment with rhIGF-1, or had previously been treated with rhIGF-1 by a qualified practitioner, and are deemed to have SPIGFD as per the approved rhIGF-1 label (European Medicines Agency (EMA) 2025 [19] and the Food and Drug Administration (FDA) 2025 [20]. It should be noted that the treating physician sets the diagnosis and given that national growth charts differ and that IGF-I assays are heterogenous and have different age and sex dependent reference ranges, the diagnostic criteria are not coherent. It is important to note that the inclusion criteria in the European (Eu)-IGFD Registry, that preceded the Global IGFD Registry, were broader, and all patients aged between 2 and 18 years with growth failure, with or without SPIGFD, and starting to or receiving rhIGF-1 therapy could be included [17]. Given that the Global IGFD Registry is an extension of the Eu IGFD Registry, some patients included in the Global IGFD Registry were not reported to have SPIGFD. Children entering the registry are required to give informed consent, where appropriate, in addition to mandatory consent from their parents or legally authorized representatives. Children participating in a clinical trial for short stature or rhIGF-1, with any contraindication to rhIGF-1 as per the approved label, or with medical history of neoplasia or closed epiphyses are excluded. The Global IGFD Registry is conducted in compliance with independent ethics committees/institutional review boards, informed consent regulations, the Declaration of Helsinki, International Conference on Harmonization, and Good Epidemiological Practice Guidelines.

Data were collected using an electronic case report form, which included clinical data from patients' medical records, and comprised baseline characteristics, treatment outcomes, auxological parameters, including HtSDS at baseline and NAH, and treatment-emergent adverse events (TEAEs). Several sub-groups of children, that we refer to in this review, have been previously described in detail [17,18,21–23].

2.2. Safety analysis

Targeted treatment-emergent adverse events (TEAEs) [17] were defined as AEs occurring while treatment was ongoing, which were either frequently or historically associated with rhIGF-1 therapy (regardless of whether they were considered drug related).

2.3. Statistical analysis

The main effectiveness endpoints, i.e. first and subsequent years of HtSDS changes from baseline (ΔHtSDS) and height velocity, as well as HtSDS and HtSDS gain from baseline to NAH are reported. HtSDS as well as weight and BMI SDS were calculated adjusted for sex and age as previously described [17]. For France and southern European countries, height and weight SDS were calculated using Sempé reference means and SD values and, 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 (17).

2.4. Subgroups of interest in the Global/EU IGFD registry

In order to obtain an unbiased observation of height response to treatment during the first year and cumulative height responses over time and to NAH, it is a requirement that children are not treated with other growth promoting treatments prior to initiation of treatment with rhIGF-1 in the registry. Therefore, patients naïve to treatment – about 1/3 of children - are the subgroup of interest. Likewise, children that are already in their pubertal growth spurt cannot be evaluated since the catch-up growth associated with rhIGF-1 treatment initiation, cannot be separated from height acceleration or des-acceleration associated with the pubertal growth spurt. Therefore, naïve to treatment and prepubertal (NPP) children are the group of interest when assessing short- and long-term gain in height SDS. Most of the children included in the registry are reported to having a primary diagnosis of SPIGFD (about 85%). However, some of these children are reported to also have a secondary diagnosis, which may include conditions known to be associated with primary IGFD (such as Noonans syndrome) or acquired IGFD (such as Type 1 diabetes). Although such children need to be excluded, since their secondary diagnosis may affect their height response, this has not yet been done in our publications. Furthermore, it should be noted that reclassification of diagnosis, common in many rhGH treatment publications, have not been performed. One reason is that IGF-I assays are heterogenous over reporting centers/countries and another being that conversion from microgram per liter to SDS or percentiles is not always possible or meaningful. Furthermore, height SDS derived from national growth charts differs from those from the two reference populations that we have used to calculate age and sex related height SDS for Southern and Northern European countries. In pubertal children, height SDS conversions are not meaningful. The remaining children, who are not SPIGFD, have PIGFD or other conditions associated with GH insensitivity. In the latter group, the patients have no clear indication for rhIGF-1 therapy and, in some cases, pre-malignant conditions are present, and contribute to some of the more severe adverse events including neoplasms.

Further subgroups of interest are children with Laron Syndrome; confirmed in the registry by a reported GHR gene defect. They may be NPP (NPP-LS) and are in some cases included in the NPP group and not in other cases (NPP-nonLS). The NPP group, even after exclusion of LS, are largely heterogeneous, and to define NPP-responders and NPP-non-responders, we have used the median response in the registry population (First year gain in HtSDS equal to 0.3) as the cut-off level.

We have compared NPP children with previous GH treatment to NPP children naïve to treatment and we have assessed height SDS gain from initiation of treatment to near adult height (NAH) in rhIGF-1 treated children that have reached NAH.

3. rhIGF-1 treatment effects on height

3.1. Mechanism of GH and IGF-I actions on linear height

IGF-I acts through the IGF1R on growth plate chondrocytes to enhance cell mitosis, differentiation and to control apoptosis. These actions impact on the fetal/infancy, the childhood and the pubertal growth phases, although the regulation of IGF-I gene expression (and growth) is under GH control not until during the end of first year of life as reviewed elsewhere [9]. In the fetal/infancy growth phase, IGF-I and IGF-II contribute equally to linear growth and insulin plays a similarly important role. During the first year of life, the IGF-I gene becomes GH regulated, and this also applies to the IGFBP-3 and ALS genes. The gene products, IGF—I, IGFBP-3 and ALS form ternary complexes with a long half-life in serum and with less bioavailability. This is the main reason for the increasing total concentrations of IGF-I during the first year of life coinciding with decreasing linear growth velocity. In children with complete GH insensitivity, such as children with Laron Syndrome, appropriate rhIGF-1 treatment does not restore total IGF-I levels in serum due to concomitant IGFBP-3 and ALS deficiency. On the other hand IGF-I bioavailability is increased in the absence of ternary complex formation [24]. GH itself has IGF-I independent effects on linear growth via the GHR enhancing cell mitosis and differentiation in stem cells of the growth plate and thereby giving rise to IGF-I responsive growth plate chondrocytes. This is particularly important to note in the context of total GH insensitivity and contributes to the failure of patients with Laron Syndrome, appropriately treated with rhIGF-1, to obtain a normal adult height. During childhood and pubertal growth phases, generation of IGF-I- by GH is possible only if the individual is in the fed state. Insulin is the mediator of this permissive effect by facilitating GH signaling via the GH receptor. During puberty, sex steroids allow GH and consequently IGF-I secretion to increase by relaxation of the negative feedback of IGF-I on hypothalamic and pituitary levels. Toward the end puberty, increasing levels of estradiol in girls and boys induces senescence in the stem cells of the growth plate and the individual reaches adult height. In S Yakar's review [25] in this special issue, actions of growth factors on the growth plate are described in further details.

3.2. First year height response

In the first published report from the IGFD registry [17] the first year HtSDS response in the registry population ($n = 144$) starting Increlex therapy with a median (25th,75th percentile) HtSDS of −3.0 (−3.8, −2.1) and at a median (IQR) age of 10.6 (6.8, 13.2) years was reported to be 0.3 ± 0.4. These results and those to follow are presented in Table 1 for comparison. The HtSDS response in the NPP subgroup of patients remaining prepubertal during the first year ($n = 67$) and starting therapy with a HtSDS of −3.1 (−3.7, −2.4) and at an age of 8.3 (5.8, 11.2) years was 0.5 ± 0.4. Catch-up growth during the first year of rhIGF-1 therapy is larger than in subsequent years and therapies with other growth promoting drugs affecting growth may impact on first year response to rhIGF-1. Given that the registry collects data from the beginning of Increlex treatment, there are patients in the registry population that have received rhGH treatment (see below how this affects HtSDS gain), other preparations of rhIGF-1 and/or other drugs affecting growth and therefore their first year HtSDS response is affected by these treatments.

A subgroup analysis from the IGFD registry was published [18] with effectiveness data restricted to the NPP group and excluding patients with Laron Syndrome (NPP-nonLS; $N = 88$); Table 1. Starting therapy with a HtSDS of −3.26 (−3.82; −2.88) and at an age of 8.23 (5.70; 11.21) years, HtSDS gain was 0.37 (0.28; 0.45). NPP-LS patients ($N = 10$) starting therapy with a HtSDS of −5.88 (−6.89; −4.22) and at an age of 6.11 (2.82; 8.30) years had a HtSDS gain of 0.70 (0.29; 1.10). In this paper we noted a large variability in height response in NPP-nonLS patients and reported that in more than half of the NPP-nonLS patients who had a HtSDS gain >0.3 ($N = 50$) the median (IQR) HtSDS gain was 0.64 (0.57; 0.71), not different from that in the NPP-LS group. This suggests that it is very important to consider if patients have baseline characteristics associated with a good response to treatment. Young age at baseline was a positive independent predictive factor of HtSDS response in the NPP-nonLS group (0.75 (0.65;0.87) estimated difference (75% CI), $p < 0.001$ as determined by multivariate regression analysis.

In Bang et al.(2015) [17] we reported a mean (SD) first year annualized height velocity (HtV) in the registry population of 6.9 (2.2) cm/yr. At ESPE 2024 we presented 41 children with prior rhGH treatment starting rhIGF-1 treatment more than 1.5 years later than in NPP children ($N = 174$) and with first year Ht SDS gain of 0.25 and 0.40, respectively ($P = 0.038$ adjusting for variables by Inverse probability of treatment weighting model).

First year annualized height velocity or change in height velocity is more dependent on age compared to gain in Ht SDS, since height velocity is strongly age dependent. Therefore, we have considered gain in Ht SDS to be the more important efficiency variable in the registry.

Age at start of treatment, was the only factor (if not considering a

Table 1
Effectiveness of treatment with rh-IGF1 in children with SPIGFD.

Reference	Study design	Subgroup analysis	Number of patients (% of total cohort)	Age at start of treatment	Ht SDS at start of treatment	First year Ht SDS gain	Dose	Treatment duration	Annualized first year Ht velocity	Subsequent years gain from baseline Median (25th, 75th percen-tile)	Ht SDS gain from treatment initiation to near adult Ht	Ht SDS at NAH and % of children with NAH > −2 SDS
				Median (25th,75th percentile) years	Median (25th, 75th percen-tile)	Mean ± SD	Mean	Years	Mean (SD)	Yr 2	(mean (SD); [95% CI]	
					Mean (SD) 95% CI	Median (25th, 75th percen-tile)		Median (IQR) or mean (SD)	[95% CI]	Yr 3		
									cm/year	Yr 4		
Bang et al. 2015 Hormone Research in Pediatrics [17]	Longitudinal cohort based on EU-IGFD registry	Registry population 84.6% are SPIGFD	N = 144	10.6 (6.8, 13.2)	−3.2 (−4.4, −2.6)	0.3 ± 0.4	Escalation to 116.0 μg/kg BID at 1.0 yr	1.0	6.9 (2.)2 [6.5; 7.2]			
		NPP subgroup	N = 67	8.3 (5.8, 11.2)	−3.1 (−3.7, −2.4)	0.5 ± 0.4			7.3 ± 2.0 [6.8; 7.7]			
Bang et al. 2021 European Journal of Endocrinology [21]	Longitudinal cohort based on EU-IGFD registry	NPP-nonLS	N = 88	8.2 (5.7, 11.2)	−3.3 (−3.8, −2.9)	0.37 (0.28, 0.45)			7.04 (1.96)	0.64 (0.51, 0.77) 0.88 (0.73, 1.02) 1.03 (0.89,1.17) 1.23 (0.57, 1.88)		
		NPP-LS	N = 10	6.1 (2.8, 8.3)	−5.9 (−6.9, −4.2)	0.70 (0.29,1.10)			8.25 (2.54)	1.20 (0.36, 2.03) 1.33 (0.33, 2.33)		
		Responder[1]	N = 50 (57% of NPP-nonLS)	6.3 (4.2, 9.3)	−3.3 (−4.0, −2.8)	0.64 (0.57; 0.71)			8.06 (1.69)	0.91 (0.77, 1.05) 1.15 (0.98,1.32) 1.21 (1.03, 1.40)		
		NPP-nonLS										
Ramon-Krauel M et al. 2025 J Clin Endocrinol Metabolism [23]	Longitudinal cohort based on EU-IGFD registry	NAH population		Boys 12.6 (3.1) Girls 10.3 (3.4)	−3.6 (1.4) −3.9; −3.4			3.9 2.3; 6.0			0.9 (1.1)	−2.8 (1.7) And 33.3
		All	N = 92									
		NPP	*N* = 41	Boys 10.8 (3.3) Girls 9.2 (3.1)	−3.6 (1.4) −4.0; −3.1			4.7 3.5; 7.0			1.4 (1.0) [1.1; 1.7]	−2.2 (1.4) And 46.7
		LS	N = 18 (N = 3 was NPP)	Boys 15.0 (2.6) Girls	−5.0 (1.8) −5.9; −4.2			4.6 2.1; 7.3			1.0 (1.1) [0.4; 1.6]	−4.1 (1.9) And 10.5

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Table 1 (*continued*)

Reference	Study design	Subgroup analysis	Number of patients (% of total cohort)	Age at start of treatment	Ht SDS at start of treatment	First year Ht SDS gain	Dose	Treatment duration	Annualized first year Ht velocity	Subsequent years gain from baseline Median (25th, 75th percen-tile)	Ht SDS gain from treatment initiation to near adult Ht	Ht SDS at NAH and % of children with NAH > −2 SDS
				Median (25th,75th percentile) years	Median (25th, 75th percen-tile)	Mean ± SD	Mean	Years	Mean (SD)	Yr 2	(mean (SD); [95% CI]	
					Mean (SD) 95% CI	Median (25th, 75th percen-tile)		Median (IQR) or mean (SD)	[95% CI]	Yr 3		
									cm/year	Yr 4		
				9.9 (4.7)								
		NPP-LS	N = 3	2 to 8 yrs							Range 1.4 to 3.3	
Klinger & Laron. 1995 Journal of Pediatric Endocrinology & Metabolism, [26]	1-yr, randomized, open-label trial	Laron	N = 9	7.4 (1.7) Range: 0.5 to 14.6	−5.7 (0.5)		50–200 μg/kg once daily		4.7 (1.3) to 8.2 (0.8)			
Guevara-Aguirre et al. 1995 J Clin Endocrinol Metab [27]	RCT		*N* = 7 (rhIGF-1) vs.	4–16 yrs				1 yr rhIGF-1 vs. 0.5 yr placerbo/ 0.5 yr rhIGF-1rhIGF-1 after 0.5 yr placebo	2.9 (0.6) to 8.8 (0.6) to 8.9 (0.7) vs.			
	rhIGF-1 /placebo	Laron Syndrome	N = 9 (placebo 0.5 yr and rhIGF-1 last 0.5 yr	of age in IGF vs Placebo (NS)	Not reported	Not reported	rhIGF-1120 μg/kg BID vs. placebo/ rhIGF-1120 μg/ kg BID		2.8 (0.3) to 4.0 (0.7) to 8.7 (0.6) (annualized baseline to 0.5 yr to 1 yr)			
Guevara-Aguirre et al. 1997 J Clin Endocrinol Metab [32]	Continuation of the 1995 RCT study	Laron Syndrome	*N* = 15 (120) vs. N = 7 (80)	9.8 (3.4) yrs. (120)vs. 7.6 (4.7) yrs. (80)	−8.5 (1.3) (120) vs. −8.0 (1.8) (80)	1.4 (0.6) (combined 120 and 80 over 2 yrs)	120 μg/kg BID vs. 80 μg/kg BID	120 yr 1 yr 2 yr 3 vs. 80 yr 1 yr 2	8.8 (1.1) 9.1 (2.2)	6.4 (1.1) 5.7 (1.4) 5.6 (2.1)		
Guevara-Aguirre et al. 2013 J Clin Endocrinol Metab [38]	randomized dosing study	Laron Syndrome	N = 14 (120) vs. N = 7 (80)	3.2 to 15.9 yrs vs. 3.2 to 16.7 yrs	N = 14: −5 to −10.7 N = 7: −7.2 to −10.2		120 μg/kg BID vs. 80 μg/kg BID	120 Baseline yr 1 yr 2 yr 3 vs.	3.2 (1.3) 8.4 (1.4)	6.6 (1.2) 5.6 (2.0)		

(*continued on next page*)

Table 1 (*continued*)

Reference	Study design	Subgroup analysis	Number of patients (% of total cohort)	Age at start of treatment	Ht SDS at start of treatment	First year Ht SDS gain	Dose	Treatment duration	Annualized first year Ht velocity	Subsequent years gain from baseline Median (25th, 75th percen-tile)	Ht SDS gain from treatment initiation to near adult Ht	Ht SDS at NAH and % of children with NAH > −2 SDS
				Median (25th,75th percentile) years	Median (25th, 75th percen-tile)	Mean ± SD	Mean	Years	Mean (SD)	Yr 2	(mean (SD); [95% CI]	
					Mean (SD) 95% CI	Median (25th, 75th percen-tile)		Median (IQR) or mean (SD)	[95% CI]	Yr 3		
									cm/year	Yr 4		
									80			
									Baseline			
									yr 1 3.0 (1.8)			
									yr 2 9.1 (2.2)			
										5,6 (2.1)		
										5.9 (2.3)		
M B Ranke 1995 Horm Res [28]	Open-label design, uncontrolled, clinical trial	GHIS and GH1 gene defect (*N* = 2)	*N* = 26	9.8	−6.4 (1.7)	+0.89 (0.41)			3.9 (1.8) to 8.5 (2.1)			
Ranke et al1999 Horm Res [36]	Open-label design, uncontrolled, clinical trial	GHIS and GH1 gene defect (N = 2)	N = 26	10.8 (3.9) (range 3.7–19.6),	−6.8 (1.6)	+0.69 (0.46)						
Chernausek et al. 2007 J Clin Endocrinol Metab [29]	Open-label design, uncontrolled, clinical trial		*N* = 76				>100 μg/kg (designated to 120 μg/kg		2.8 (??) to 8.7 (1.7)			
Backeljauw et al. 2013 Horm Res Paediatr [39]		SPIGFD,										???
	Open-label design, uncontrolled, clinical trial	9/22 had GnRHa for mean 2.3 yrs. (N = 5 was GH gene defects w antibodies)	N = 21	7.4 (4.7)	−6.6 (2.1)		Mean 113 μg/kg BID	10.0 (range 3.6–19.3)			Mean + 1.9 (range + 0.1 to +4.7)	and
												3 / 21
Midyett et al. 2010 J Clin Endocrinol Metab [30]	1-yr, randomized, open-label trial	PIGFD (Ht SDS < −2, IGF-I SDS < − 2, GH >7)	Untreated *N* = 23	7.0 (2.4)	−2.8 (0.7)	0.02 (0.2)						
			80 μg BID *N* = 40	7.7 (2.4)	−2.7 (0.5)	0.4 (0.2)						
			120 μg BID *N* = 45	7.6 (2.7)	2.9 (0.8)	0.5 (0.3)						

[1] First year HtSDS gain >0.3.

diagnosis of Laron syndrome as a variable or when excluding Laron children from analysis) independently associated with first year gain in HtSDS in a multivariate analysis [21]. However, it should be considered that starting at a young age is more likely if HtSDS is severely affected already at a younger age. As mentioned, having a diagnosis of Laron Syndrome (or a more severe SPIGFD phenotype) combines young age at diagnosis and start of rhIGF-1 treatment and a baseline Ht SDS, that is very low despite the young age.

The finding that patients with LS have a better first-year height response (HtSDS gain as well as HtV) agrees with previous clinical trials (Table 1). Generally, a better first year Ht response was found in clinical trials of patients with LS [26,27] than in clinical trials with a population defined by biochemical characteristics of GHIS [28,29] and with a poorer response with less strict criteria [30]. Some of these studies include children in puberty. The variation in the first year Ht response to treatment is large in all published studies and most likely extends to more variables than those considered to identify response. Variable phenotype, and in children with Laron Syndrome, genetic variability, is likely to contribute to variability in first year height response. Variable phenotype is likely to be more pronounced in the registry population since there is no strict control that the diagnostic criteria apply at inclusion and growth charts and GH/IGF-I assays are heterogenous. Furthermore, LS children included in the registry are likely to be genetically heterogenous, although sequencing data are not collected. The Ecuadorian cohort is genetically homogeneous with an alternative splice mutation at the third position of codon 180 in exon 6 of the GH receptor gene [31] and their auxology and biochemical characteristics are less variable [5]. Despite their phenotypic homogeneity, the first-year height response was largely variable with annualized height velocity ranging from approximately 7 to 11 cm/yr (first half-year on treatment) and approximately 5–11 cm/yr (second half-year in treatment) in 7 subjects [27]. Given that the baseline age and height velocity varied, these factors are likely to impact on the height response in this genetically and phenotypically homogenous cohort.

Dose was suggested to impact on the growth response in the study by Chernausek 2007 [29] by demonstrating a linear correlation of the first year annualized height velocity with the average dose, ranging from 40 to 120 μg/kg BID. However, further analysis of the impact of additional factors by multivariate analysis was not performed and may not have been possible given the small number of subjects. In the Ecuadorian RCT, also with a small number of patients but randomized to either 80 or 120 μg/kg BID, there was no significant effect on HtSDS gain during the first year of treatment [32]. We have not been able to identify dose as a predictor of first-year response to treatment in our larger NPP cohort of children in the global IGFD registry [24]. On the other hand, less severe PIGFD patients in the RCT by Midyett et al. [30] demonstrated a higher height velocity with the 120 μg/kg BID vs the 80 μg/kg BID dose and with an inverse association with age.

It is evident that the catch-up in prepubertal SPIGFD children treated with rhIGF-1 are not as marked as in severe GHD patients receiving rhGH [32]. Some factors have been identified to explain this. First of all, GH has IGF-1 independent effects on growth by stimulating stem cells in the growth plate. Secondly, the lack of the GH dependent proteins IGFBP-3 and ALS, which also impact IGFBP-5 circulating levels, has been proposed to explain that total levels of IGF-1 remain low during rhIGF-1 treatment [33]. However, formation of ternary complexes decreases IGF-1 availability. For example, in the human fetus and newborn, total IGF-1 circulating levels are low and so are the levels of IGFBP-3 and ALS. Despite that IGF-1 circulates predominantly in binary complexes bound to other IGFBPs than IGFBP-3 with absence of ternary complexes [34], height velocity is faster in the fetus and first year of life than later in life. Further evidence that IGF-I are contained in the ternary complex and have low bioavailability comes from the report of short stature in children with PPAP2A defects associated with inability to proteolyze IGFBP-5 and IGFBP-3 and thus inadequate release of IGF-I from ternary complexes [35]. These observations would argue that absence of ternary complexes in rhIGF-1 treated children with SPIGFD are not impairing catch-up growth.

3.3. Subsequent years height SDS gain

First year Ht SDS gain is greater than the gain in subsequent years. We have published accumulated HtSDS gains for different subgroups in the first and subsequent years for up to 5 years of treatment in our 2015 paper, our 2021 paper and with the highest number of patients in our 2024 years ESPE poster – summarized in Table 1. The mean gain in HtSDS (N) in the NPP group versus the NPP-LS were 0.40 (144) vs. 0.65 (17), 0.77 (124) vs. 1.21 (15), 1.00 (98) vs. 1.19 (14), 1.17 (78) vs. 1.42 (14) and 1.30 (57) vs. 1.60 (12) after 1, 2, 3, 4 and 5 years of treatment, respectively. This corresponds to a height velocity in NPP vs. NPP-LS children of 4.70 vs. 5.36, 7.22 vs. 8.01, 6.32 vs. 7.06, 5.89 vs. 5.78, 5.47 vs. 5.39 and 5.27 vs. 5.51 at baseline, and during the first, second, third, fourth and fifth year of treatment.

Our data on subsequent years growth on rhIGF-1 are in accordance with treatment beyond the first year in studies from Guevara-Aguirre 1997, Ranke 1999, Chernausek 2007 (29,32,36) demonstrating attenuation of height gain/height velocity in subsequent years – see Table 1. It is a common feature of catch-up growth that height gain decreases in subsequent years until the expected parental height SDS is obtained. It is observed with spontaneous catch-up growth in prepubertal children after successful treatment of a disease state or after hormone substitution in deficiency states such as thyroxine substitution in thyroid hormone deficiency or more extensively studied in rhGH substitution treatment in GH deficient prepubertal children. Even pharmacological treatment of various short stature conditions with approved indications for rhGH other than severe GHD, have the greatest gain in height during the first year. It is possible that the dynamics of catch-up growth may differ to some extent depending on the underlying problem. This may be true in different individuals given the heterogeneity of phenotypes in the registry with several pathologies causing SPIGFD and/or at different severity of patients with similar pathology. One example of different dynamics of the catch-up growth process is found in patients with Achondroplasia treated with antagonist of the C - natriuretic peptide receptor-2 (NPR2) [37]. In the registry, where particularly poor responders or those with adverse events stop treatment earlier, the dynamics are more difficult to study. Ideally, the same individuals should contribute to analysis throughout the observation period. However, this is not the way that data from the registry has been reported.

Interestingly, the long term dosing study on rhIGF-1 treatment in LS from Guevara- Aguirre et al. [38] found no significant difference in HtSDS gain or height velocity in 21 patients aged between 3.2 and 15.9 yrs. treated with either 80 or 120 μg/kg BID. Importantly, bone age was advanced by 3.3 ±1.3 yrs. in the high dose group and more than 1.8 ±0.75 yrs. in the lower dose group, indicating that higher dose may compromise adult height. The authors also found that reduction of body fat was less pronounced in the high dose group (further discussed in the glucose metabolism chapter) and suggested this one potential explanation was a faster acceleration of bone maturation. However, rhIGF-1 treatment also impacts on timing of puberty as discussed below.

The limitations in the assessment of registry data on height SDS gain

or annualized HtV in consecutive years of treatment also applies to many of the clinical trials. In some of the trials, there was a stricter first-year protocol, while continuation of treatment was offered as 'compassionate use' kind of programs and data was collected with considerable loss of subjects/data with time.

3.4. Near adult height (NAH) and total HtSDS gain from baseline to NAH

We reported NAH height data from 102 of 324 children included in the Global IGFD registry in our most recent publication [23]. The reason for stopping treatment was attainment of NAH in 59 children and other causes in 43 children. The primary diagnosis was reported to be SPIGFD in 85.3% of the children in the overall population and 88.9% in the NPP population. Only 3 of the LS children were NPP. At initiation of treatment, boys had a mean (SD) age of 12.6 (3.1) yrs. and girls 10.3 (3.4) yrs. The NPP children were younger with boys being 10.8 (3.3) yrs. old and girls 9.2 (3.1) yrs. old. Most of the LS children had been treated previously with IGF-I ($N = 11$) or GH ($N = 4$), and particularly the LS boys were older (15.0 (2.6) yrs. old), while LS girls were 9.9 (4.7) yrs. old). LS children were shorter at initiation of treatment (−5.0 (1.8) SDS) compared to NPP (−3.6 (1.4)). It was more common that LS children were treated with gonadotropin-releasing hormone (GnRH) agonist (15%), compared to 6% and 2% of children in the overall and NPP populations. The mean (SD) gain in HtSDS from initiation of treatment to NAH was 1.4 (1.0) in the NPP population and the range in the three NPP-LS children was 1.4 to 3.3. This endpoint may be the most important efficiency variable but is not relevant in groups of children who received treatment prior to baseline or who have started treatment after start of puberty (total NAH population). Ht SDS at NAH was −2.2 (1.4) in NPP with 46.7% of children above −2 SDS and markedly lower in the overall NAH population (including non-NPP patients) −2.8 (1.7) with 33.3% of children (most of them NPP) above −2 SDS. To some extent this supports the findings that we recently presented (abstract at ESPE 2024) that short term Ht responses in prepubertal and previous GH treated patients is less than in NPP. The Ht SDS at NAH in LS was −4.1 (1.9) with 10.5% of children within the normal range. This result should be viewed in the context of a lower Ht SDS at initiation of treatment despite a better first and consecutive years Ht SDS gain in LS.

NAH data is reported from the registry [23] for $N = 92$ subjects and by Backeljauw [39] for $N = 21$ subjects – see Table 1. The subjects in the latter publication had a more severe phenotype with a Ht SDS of −6.6 (2.1) at baseline and treatment was started later than what may be considered optimal but at least at a relatively younger age of 7.4 (4.7) yrs. compared to NPP children from the registry. In the registry, the group with a similarly severer phenotype is the $N = 18$ children in the LS subgroup. However, most of these children received previous treatment and the initiation of rhIGF-1 treatment in the registry were started very late in boys (15.0 (2.6) yrs. of age) and girls (9.9 (4.7) yrs. of age). Previous treatment was rhIGF-1 from other providers in the majority of cases ($N = 11$). The height at treatment initiation does not reflect the severity of their phenotype given that those with previous rhIGF-1 treatment already had most of their treatment catch-up. It is not clear why four LS children had previous rhGH but most likely the correct diagnosis was delayed in those children. Only 3 of these children were NPP-LS starting at a more appropriate age.

In our report [23], HtSDS gain was only half of that in the Backeljauw 2013 publication. However, only comparison between Ht SDS at NAH is appropriate, given that previous treatment was given in many children in our study. Unfortunately, there is no data on Ht SDS at NAH in the Backeljauw study but 3/21 reached a Ht SDS > 2, which is similar to our report, where 10% reached a height within the normal range and a mean (SD) Ht SDS at NAH of −4.1 (1.9). Although this may seem to be a poor result, it enables most treated LS patients to function in a psychosocial context [13].

Our report is the first report of NAH in less severe SPIGFD treated with rhIGF-1. A total height gain in the NPP group of 1.4 (1.0) enabled almost 50% of subjects to reach a HtSDS within the normal range and this is a result that is similar to NAH in subjects with the most indications for rhGH treatment except severely GHD patients. This result is also relevant for most children responding to rhIGF-1 treatment during the first year (NPP-responders) given that these children are more likely to continue treatment than those with a poor response (HtSDS gain less than 0.3 during the first year).

4. rhIGF-1 treatment effect on pubertal timing and growth dynamics

4.1. Mechanism of GH and IGF-I actions on puberty

Initiation of puberty is associated with increased GnRH secretory peaks and subsequent release of LH/FSH leading to stimulation of gonadal growth and steroidogenesis. Steroidogenesis is dependent on a normal GH-IGF-axis [40]. Increased GnRH release stimulated by IGF-I [41] may be part of the nutritional input, which also involves Leptin and Kisspeptin. Even at the pituitary level IGF-I influences LH release via Kisspeptin [42]. Consequently, IGF-I deficiency, whether it is secondary to GHD or primary in SPIGFD, is associated with a delayed puberty start as reported by Laron [43,44]. The finding of underdeveloped genitalia and gonads [43,44] suggest that IGF-I deficiency may influence fetal sexual differentiation and development including the mini-puberty. The pubertal growth spurt is associated with a pubertal IGF-I peak that involves relaxation of the negative feedback on GH release induced by sex steroids [45]. A more detailed understanding were needed of how SPIGFD influences two important characteristics of the growth spurt at puberty; the pubertal peak height velocity (PPHV) and the age at which the PPHV occurs, until our publication from the registry [18].

4.2. Pubertal timing

Using data from 213 rhIGF-1 treated children who were prepubertal (Tanner 1 (T1); Breast Tanner 1 (B1) for girls and Genitalia Tanner 1 (G1) for boys) at first rhIGF-1 administration, we analyzed the age at the last registration of T1 and the first registration of B2/G2 as well as later Tanner stages and corresponding HtV data [18]. More than 50% of the children had a dose of 120 μg/kg BID and the mean dose was stable throughout puberty. Patients receiving gonadotropin-releasing hormone agonists were excluded. Normative data from Juul et al. [46] was used for comparison. In boys the mean (SD) age at last registration of T1 and first registration of T5 was 13.0 (2.0) and 16.3 (1.6) years, respectively, indicating a delay at puberty start of 1.5 years and 1.0 years delay at T5 entry. In girls it was 11.6 (1.8) and 14.7 (1.5) years, respectively, indicating a delay at start of puberty of 1.2 years but a faster tempo of pubertal development with entry at T5 at a similar age as in the controls. A total of 36 children entering T5 contributed with data and in this subgroup, there was only a slight delay in boys at start of puberty (0.7 years difference) and no delay entering T5 and in girls similar ages at entry of T2 and T5. The average duration of puberty was 3.7 years for boys and 3.9 years for girls.

4.3. Pubertal growth dynamics

During a shorter period of pubertal growth spurt (T2 delayed more than entering T5), rhIGF-1 treated children appeared to gain height: HtSDS increased 0.3 SDS in boys from the last registration of T1 to entering T5 while girls increased 0.8 SDS, during their shorter pubertal growth spurt. However, children with delayed T2 will lose HtSDS compared to the mean Ht SDS curve (cross- sectional data including children with puberty start at any age) and will thus appear to gain HtSDS when reaching the end of puberty. In the subgroup of 36 children, contributing with data until the end of puberty, the data were similar with a 0.5 SDS increase in boys and a 0.8 increase in girls.

Data from rhIGF-1 treated puberty population ($N = 213$) demonstrated that pubertal peak height velocity (PPHV) occurred in T3 for boys and T2 for girls and was on average 2 cm/year lower than mean PPHV in controls [47]. Mean age at the maximum height velocity was 15.1 years in boys ($N = 52$) and 13.4 years in girls ($N = 35$). Puberal height gain between T2 to T5 was 18.4 cm (10.7–33.3) cm in boys and 15.6 cm (6.0–18.4) in girls compared to normative values of 25–30 cm in boys and 20–25 cm in girls – with children starting puberty relatively late having pubertal height gains in the lower end of this range.

Laron et al. [43,44,48] have reported that untreated children with Laron syndrome have underdeveloped genitalia at birth and are delayed in puberty, particularly in boys. However, a thorough analysis of pubertal timing and growth dynamics in Laron or SPIGFD children with ongoing rhIGF-1 treatment have not been published before our publication [18].

Given that HtSDS during pubertal years are derived from cross-sectional data, control children who enter puberty late will have a relatively low HtSDS prior to pubertal entry (last registration at T1). Control children who enter puberty late will have a lower pubertal peak height velocity and gain less height (in cm) but will gain more HtSDS during pubertal years. This may at least partly contribute to our findings in registry children with relatively late puberty start.

In summary, rhIGF-1 treatment in children with SPIGFD may not completely normalize the age of puberty start. The tempo of pubertal progression is relatively normal or slightly increased in girls. PPHV occurs as in controls in T3 for boys and T2 for girls, but the total height gain in cm is less than expected even when considering that late puberty start will diminish height gain in controls. rhIGF-1 treatment in children with SPIGFD secures a gain in HtSDS from last registration of T1 to T5, however, this is expected in children starting puberty relatively late.

5. rhIGF-1 treatment side-effects on glucose metabolism

5.1. Mechanism of GH and IGF-I actions on glucose metabolism

IGF-I acts through the IGF1R to increase glucose uptake in muscle [49] and is equipotent to insulin in the absence of IGFBPs [50]. After iv-injection in adults IGFBPs attenuates the glucose lowering effects of IGF-I to 13.5 times less than those of insulin [51]. Following a subcutaneous injection of rhIGF-1, there is a lag phase and then an increase in IGF-I determined by microdialysis that can be detected in peripheral tissues including muscle expressing the IGF1R (and adipose tissue with no expression of IGF1R in mature adipocytes) [52]. A simultaneous increase in muscle tissue levels of IGF—I, and an increase in glucose uptake can be detected simultaneously [52]. GH has opposite effects on glucose metabolism compared to IGF—I. GH induces lipolysis in adipose tissue and increases glucose production via liver gluconeogenesis as well as by fatty acid activation of PPAR-gamma [53]. In addition, GH induces insulin resistance through several pathways including activation of SOCS [54]. In healthy subjects GH effects on glucose homeostasis is balanced by IGF-I effects. Uncoupling of the GH stimulated IGF-I gene expression during fasting, resulting from lack of insulin enhancing effects on GH signaling via the GHR, is important in preventing hypoglycemia. Growth hormone actions in the absence of IGF-I (for example resulting from an IGF-I gene defect) in the fed state results in raised demands on insulin production to obtain glucose homeostasis, and the resulting hyperinsulinemia is perceived as insulin resistance [55]. Although IGF-I effects on glucose metabolism are physiological and required for normal glucose homeostasis, the effects in patients with GH insensitivity are unbalanced and increase the risk of hypoglycemia. Individuals with SPIGFD and absent GH effects are prone to develop hypoglycemia particularly in the newborn and young. Indeed, spontaneous hypoglycemia is common in Laron syndrome/SPIGFD particularly in the newborn and young [29,56]. Furthermore, treatment with rhIGF-1 increases the risk of hypoglycemia particularly in the absence of appropriate food intake [24,57]. Increasing IGF-1 in the circulation in the absence of GH dependent IGFBP-3 and ALS may have impact on free circulating IGF-1 [11]. On the other hand, GH independent binding proteins such as IGFBP-1, −2, −4, −5 and − 6 are sufficient to prevent excess IGF-I in the fetus and newborn [22].

5.2. Hypoglycemia

In the first report from the EU-IGFD registry, 195 patients were included (mean time on treatment close to 800 days) and we reported that hypoglycemia, a targeted adverse event (TEAE) in the registry, occurred in 17.6% of children. Each child with hypoglycemia had on average two hypoglycemic events and less than half of the events were documented with a capillary blood glucose measurement [17]. Less than 3% of children were reported to have serious events (causing convulsions, consciousness or hospitalization). Having a hypoglycemic event was associated with age at baseline and with having a diagnosis of Laron syndrome, but was not associated with dose at the time of hypoglycemia or time on treatment.

In a later publication [21], data on 242 children was reported and hypoglycemia was found to be most common in naïve to treatment, prepubertal (NPP) children with Laron syndrome (LS) (50% of the children), less common in NPP-nonLS responding to treatment (25% of the children) and with the lowest frequency in NPP-nonLS poor responders (15% of the children).

In the most extensive analysis of hypoglycemia in patients treated with rhIGF-1 [22] so far, we reported data from 304 patients with a total of 132 hypoglycemic events reported in 80 patients (26.3%). Hypoglycemic events were classified as mild (78 AEs), moderate (35 AEs) or severe (9 AEs) and 10 were not classified. In 8 children (2.6%), 13 hypoglycemic events were classified as serious. A limitation in the registry electronic CRF related to reporting hypoglycemic events is that only single events can be registered and it is not possible to report a frequency of reoccurring milder events. Therefore, milder events are likely to be underreported. About half of the reported hypoglycemic events were confirmed by capillary blood glucose testing.

Interestingly, children with a hypoglycemic event had a median treatment duration of 188.0 days at the time of the event and a median rhIGF-1 dose of 100.0 μg/kg BID. A number of variables, including treatment time until and dose at the time of the event, were not associated with risk of having a hypoglycemic event. Having a history of hypoglycemia prior to start of rhIGF-1 therapy and having a diagnosis of Laron syndrome were the only variables associated with increased risk in a multivariate regression analysis. The mean first year mean HtSDS gain was similar between patients who experienced hypoglycemia and

those who did not.

The number of hypoglycemic events was 0.11 per patient and treatment year and the number of serious hypoglycemic events was 0.01 per patient and treatment year, considerably lower than in children with type 1 diabetes. Still, a total of 16 children (5.3%) stopped treatment permanently due to (or as a contributing factor) experiencing a hypoglycemic event.

In the EU/Global IGFD registry, hypoglycemia is the most frequently reported adverse event associated with rhIGF-1 treatment [17,18,21]. This is in accordance with previous reports in clinical trials [27,29,39]. As expected, reporting of adverse events in the registry do not capture as many hypoglycemic events (26.3% of children) compared to the events reported in clinical trials. Although it is plausible that increased awareness of the risk, instructing the patient/family that injections should not be given without prior carbohydrate intake and supporting more extended use of glucose monitoring, may reduce the prevalence of hypoglycemic events, this does not seem to be a likely explanation for lower frequency of hypoglycemia. In the open-label trial by Chernausek et al. 2007 (29)49% of children with SPIGFD had hypoglycemic events (and 5% had serious events). In that study 32% of children with hypoglycemic events had a history of hypoglycemic episodes in accordance with registry data, while the occurrence was more frequent in the first months. In Ranke et al. 1995 [28] 15% of children with GHIS had confirmed hypoglycemia with a capillary blood glucose <2.5 mmol/l during the first two years of the trial. In the open-label cohort study published by Laron and Klinger et al. 1995, [26] 11 children with Laron syndrome were treated with rhIGF-1 of 150–200 μg/kg once daily. All children had a history of severe hypoglycemia in infancy and early childhood. They reported that hypoglycemic events on treatment were not increased compared to baseline. It has been argued that once daily injections may have different risks of inducing hypoglycemia compared to bi-daily injections. In that paper Laron et al. emphasized that postprandial hyperglycemia was improved by rhIGF-1 therapy. A similar observation was published later in a case report [58]. None of the clinical trials have assessed statistically independent predictive factors for hypoglycemic events.

In many centers children with SPIGFD on rhIGF-1 therapy, are monitored with glucometers or CGMS during the first weeks or months of treatment. Given that hypoglycemic events are rare and do not necessarily occur in the first weeks or months of treatment, this strategy is not evidence based. However, it may help to emphasize the importance of observing and responding to symptoms in the child on rhIGF-1 treatment suggestive of hypoglycemia. Hypoglycemic events prior to start of treatment is, apart from diagnosis of Laron Syndrome, the only independent predictor of hypoglycemic events on treatment and the history of the child should be carefully explored since some parents may not have been aware of such symptoms. The most important precaution to avoid rhIGF-1 treatment associated hypoglycemic events may be to avoid giving injections in children who have infections or who have not eaten well.

6. Concluding remarks

We have reviewed the present evidence on rhIGF-1 treatment in patients with SPIGFD from the perspective of the recent publications based on real-world data from the global IGFD registry. In the five publications, we have focused on effectiveness assessing short- and long-term height gain as well as near adult height, pubertal development and growth dynamics and safety assessing hypoglycemic events which is the most frequent targeted adverse event. We have compared our findings in a heterogenous population ranging from children with less severe phenotype to the most severe phenotype of Laron Syndrome with the current literature on rhIGF-1 treatment, including data from clinical trials in larger cohorts of patients with a more severe phenotype including a genetically homogenous cohort of Laron Syndrome children from Ecuador. Our real-world data confirms previous data on rhIGF-1 therapy and demonstrates that short and long-term height improves in a majority of children with SPIGFD. The registry data points to baseline characteristics that predicts response to therapy. Hypoglycemia is the most common adverse event in previous reports and in registry data and hypoglycemia prior to start of therapy or a diagnosis of Laron Syndrome increases the risk. Although there may be underreporting of hypoglycemia in the registry, very few events over a course of therapy are reported on an individual basis. In Table 2, we have suggested some practical recommendations on how to treat and manage a child with SPIGFD based on the rhIGF-1 (mecasermin) Summary of product characteristics (https://www.medicines.org.uk/emc/product/101145/smpc; https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021839s031lbl.pdf) and added some of the evidence from the present review.

Several aspects of treatment, not discussed in the present review, would be important to assess in larger detail in the future. For example, the registry would allow assessment of other targeted adverse events including hypertrophy of lymphoid organs causing tonsillar hypertrophy, hearing problems and sleep apnea or water retention associated with acromegalic facial features as well as intracranial hypertension and papillary oedema - the rarest but also the most serious targeted adverse event. Furthermore, faster progression of malignancies that pre-exist or that spontaneously develop while on rhIGF-1 therapy is another important aspect. Some of these adverse events are reported in previous studies, nevertheless, the EU/Global IGFD registry is a very important source of evidence for such rare adverse events.

In the EU/Global IGFD registry, the 5-year post rhIGF-1 treatment follow-up requested by the EMA and a new module to assess Quality of Life will generate new real-world data to be assessed in the future. However, there are additional aspects, some analyzed in the current literature, for which the registry and its nature of a non-interventional study, do not provide full insight. These include genetics, accurate changes in adiposity and body composition, bone health and long-term risk of common diseases such as the metabolic syndrome and cancer after rhIGF-1 treatment.

Author contribution

JS and PB wrote and revised the manuscript.

CRediT authorship contribution statement

Jannette Saavedra: Writing – review & editing, Writing – original draft, Conceptualization. **Peter Bang:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Table 2
Practical guidelines for rhIGF-1 therapy.

Based on rhIGF-1 (mecasermin) Summary of product characteristics: https://www.medicines.org.uk/emc/product/101145/smpc and https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021839s031lbl.pdf
*Evidence presented in the present review

- Discuss diagnosis and management with pediatric endocrinologist experienced in managing rhIGF-1 treatment
- Ensure adherence to indication and absence of contra-indications to rhIGF-I therapy including active or suspected neoplasia
- Referrals prior to treatment start: Fundoscopy (papillary oedema?), ENT consultation (tonsillar hypertrophy?), echocardiography, bone age, clinical photo. These investigations should be repeated whenever clinically indicated as well as at the end of treatment. Audiology and DEXA may also be helpful baseline information
- Inform the child/parents about start of treatment, expected height response* – short and long term - and potential adverse events* and how to prevent/identify them. A first-year height SDS gain of less than 0.3 should be considered a poor response and diagnosis should be re-evaluated and a decision of continued treatment taken
- Educate the child/parents in preparing the drug for injections (syringe, needle, lyophilized drug to be reconstituted) and how to give s.c. injections (rotate inj. site to prevent lipohypertrophy) shortly before or after a meal or snack. If the child is unable to eat, injections should not be given. Do not increase doses to compensate for omitted doses. Physical exercise increases the need for substantial food intake
- Prescribe a glucometer and instruct of its use and symptoms of hypoglycemia. Pre-meal measurements may be recommended the first days or weeks from start of treatment (but hypoglycemia is NOT related to time from start or to dose*). Ask parents about previous hypoglycemic symptoms. Hypoglycemia occurs more often with a history of hypoglycemia and in severe cases*. Parents should document suspected hypo's and note the reading
- Include child in the Global IGFD registry after obtaining informed consent from child and parents
- Pre-treatment labs should include a wide selection of clinical chemistry (to have baseline data in case of unexpected adverse events). A full baseline examination of the child including blood pressure and auxology should be performed at baseline and every visit thereafter
- The first dose of rhIGF-1 should be given at the outpatient clinic or ward and the child should be observed for some hours but not necessarily admitted overnight
- The dose should be individualized for each patient. The recommended starting dose of rhIGF-1 is 0.04 mg/kg of body weight twice daily. If no significant adverse reactions occur for at least one week, the dose may be raised in increments of 0.04 mg/kg to the maximum dose of 0.12 mg/kg given twice daily. This dose can in most children be obtained within 1–2 months. Prolonged dose escalations may compromise first year height gain. Doses greater than 0.12 mg/kg twice daily should not be exceeded
- Endocrine nurse contact after a few days should ensure that no unexpected problems are encountered
- Regular ped endo follow-up visits at one, three, six and twelve months are recommended during the first year of treatment and at least yearly thereafter (with endocrine nurse visits in between to check rotation of injections)
- At all visits, enquire about targeted emergent adverse events (TEAE) as well as any other possible adverse events and report to the Global IGFD registry (numbers after each TEAE is frequency of total/serious TEAE[1])
  - Hypoglycemia (25.8%/2.8%)
  - Lipohypertrophy at injection site (13.4%/0.3%)
  - Headache (10.2%/0.6%)
  - Tonsillar hypertrophy and associated AEs (9.9%/3.1%)
  - Otitis media (8.1%/0.6%)
  - Acromegalic facial changes (3.7%/0%)
  - Hypersensitivity (2.8%/0.9%)
  - Sleep apnea (2.2%0.9%)
  - Hearing loss (2.2%/0%)
  - Increased intracranial pressure/papillary oedema (0.3%/0.3%)
  - Neoplasm (2%/2%)
- At the one-year visit, first year height SDS gain should be noted and action taken if less than 0.3
- Yearly blood work-up should include blood count, liver- and kidney function tests, thyroid, lipids, calcium status. IGF-I measurements are not required (varies relative to injection time and are, in most cases, subnormal since SPIGFD causes concomitant IGFBP-3 and ALS deficiency)
- Expect that puberty start may be slightly later than average, particularly in boys. If puberty is relatively early, GnRH agonist treatment may be considered.

[1] Ramón Krauel M et al. Long-term effectiveness and safety data from the Global Increlex® Registry in patients treated with rhIGF-1: Subgroup analysis of naïve prepubertal patients and patients with Laron syndrome. Abstract at ESPE 2024.

Declaration of competing interest

Our manuscript is original and is not submitted to other journals. Jannette Saavedra don't have any conflict of interests.

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