Characteristics, effectiveness and safety data for patients with growth failure treated with recombinant IGF-1 and achieving adult or near-adult height: results from the European Increlex® Growth Forum Database registry

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BACKGROUND

- Recombinant human insulin-like growth factor-1 (rhIGF-1; mecasermin [rDNA origin] injection) is approved in Europe and the US for the treatment of growth failure due to severe primary IGF-1 deficiency (SPIGFD).[1,2]
  - Long-term therapy with rhIGF-1 improves adult height of patients with severe IGF-1 deficiency.[3]
- Following approval of rhIGF-1 in Europe, the European Increlex® Growth Forum Database (EU-IGFD) registry was established to monitor the long-term safety and effectiveness of rhIGF-1 therapy in children in clinical practice.[4]
- The EU-IGFD registry provides important real-world data and offers the opportunity to explore responses to rhIGF-1 treatment, including: baseline predictors of final adult height and the identification of patients achieving adult or near-adult height.

OBJECTIVE

- To report patient characteristics, effectiveness and safety data for children receiving rhIGF-1 for SPIGFD and achieving adult height or near-adult height.

METHODS

Study design

- The EU-IGFD registry is an ongoing, open-label, observational study monitoring rhIGF-1 therapy in children with growth failure due to SPIGFD (NCT00903110) in clinical practice. The study was initiated in December 2008 and children from 10 European countries have been enrolled.

Patients

- Patients (aged 2–17 years) could be enrolled if they were receiving (or initiating) rhIGF-1 therapy and provided informed consent.
- This analysis included patients considered as having reached adult height (last height velocity [HV] <1cm/year) by 10 October 2017 and patients who were either discontinuing therapy at adult height or discontinuing therapy for other reasons and followed until adult height.

Assessments at the cut-off date of 10 October 2017

- Data collected at baseline and during treatment included:
  - Baseline characteristics (demographic and growth parameters).
  - Duration of treatment and median rhIGF-1 dose.
  - Changes in growth parameters.
- Safety data collected included:
  - Targeted adverse events (AEs), related AEs and all serious AEs, up to completion in the EU-IGFD registry.

Statistical analyses

- Height standard deviation score (SDS) was calculated:
  - In France and southern European countries using Sempé reference values.[5]
  - In the UK, Belgium, Sweden, and Poland, using UK reference values.[6]
  - In Germany and Austria using KiGGS (German Health Interview and Examination Survey for Children and Adolescents) reference values.[7]
- Annualised HV (cm/year) was calculated using height values measured at the time point of interest and at 1 year before this time point, divided by the time interval between the 2 measurements (≥6 months and ≤18 months).
- Linear regression analysis was used to identify baseline factors predictive of change from baseline in final adult height SDS (completer population: treatment-naïve prepubertal [NPP] subgroup reported only).

RESULTS

Patients

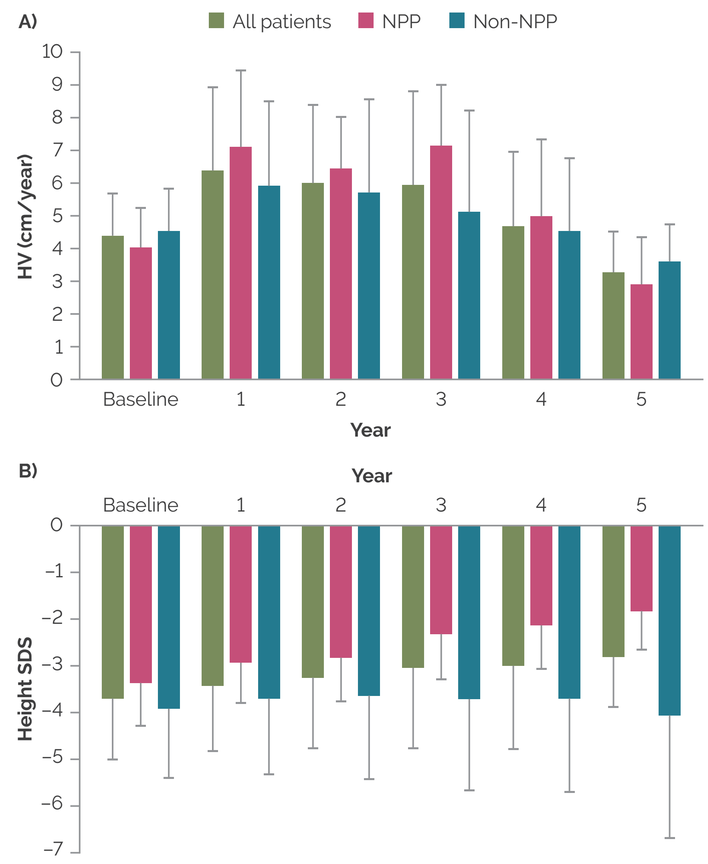
- Of 247 patients enrolled in the EU-IGFD registry (cut off: 10 October 2017), 67 achieved adult height.
- Patient characteristics at baseline are shown in **Table 1**.
- Mean (SD) age at first rhIGF-1 intake was 12.9 (2.6) years, and at the end of treatment was 16.6 (2.1) years. In total, 27 patients were NPP; 40 were non-NPP (including 1 undetermined). 85.1% patients had SPIGFD; 17.9% of whom had Laron syndrome. Most patients were pubertal stage 1 at first rhIGF-1 intake (65.6% [42/64]).

Table 1. Baseline characteristics of patients achieving adult height (completer population)

Characteristic	n	NPP N=27	n	Non-NPP* N=40	n	All patients N=67
Male, n (%)	27	15 (55.6)	40	28 (70.0)	67	43 (64.2)
Age at first rhIGF-1 intake, years	27	11.9 (2.1)	40	13.5 (2.8)	67	12.9 (2.6)
Age at treatment end, years	27	16.2 (1.9)	40	16.9 (2.1)	67	16.6 (2.1)
SPIGFD, n (%)	27	24 (88.9)	40	33 (82.5)	67	57 (85.1)
Laron syndrome, n (%)	27	0	40	12 (30.0)	67	12 (17.9)
Median (Q1; Q3) highest stimulated GH levels	22	16.8 (13.0; 26.6)	20	32.0 (16.9; 45.5)	42	21.4 (13.6; 40.0)
Height SDS at first rhIGF-1 intake	25	−3.5 (1.1)	35	−3.9 (1.5)	60	−3.7 (1.3)
HV at first rhIGF-1 intake, cm/year	11	4.3 (1.4)	25	4.6 (1.3)	36	4.5 (1.3)
Predicted adult height SDS	17	−2.2 (1.8)	18	−2.7 (2.5)	35	−2.5 (2.2)
Method for calculation of predicted adult height, n (%)	18		24		42	
Bayley–Pinneau		12 (66.7)		7 (29.2)		19 (45.2)
Tanner–Whitehouse		5 (27.8)		11 (45.8)		16 (38.1)
Other		1 (5.6)		5 (20.8)		6 (14.3)
Roche–Wainer–Thissen		0		1 (4.2)		1 (2.4)
Main reason for treatment discontinuation, n (%)	26		40		66	
Reached adult height		15 (57.7)		24 (60.0)		39 (59.1)
Lack of efficacy		4 (15.4)		5 (12.5)		9 (13.6)
Shortage of rhIGF-1		4 (15.4)		1 (2.5)		5 (7.6)
Patient/parent decision		2 (7.7)		2 (5.0)		4 (6.1)
Other		1 (3.8)		4 (10.0)		5 (7.6)
Non-compliance		0		3 (7.5)		3 (4.5)
AE		0		1 (2.5)		1 (1.5)

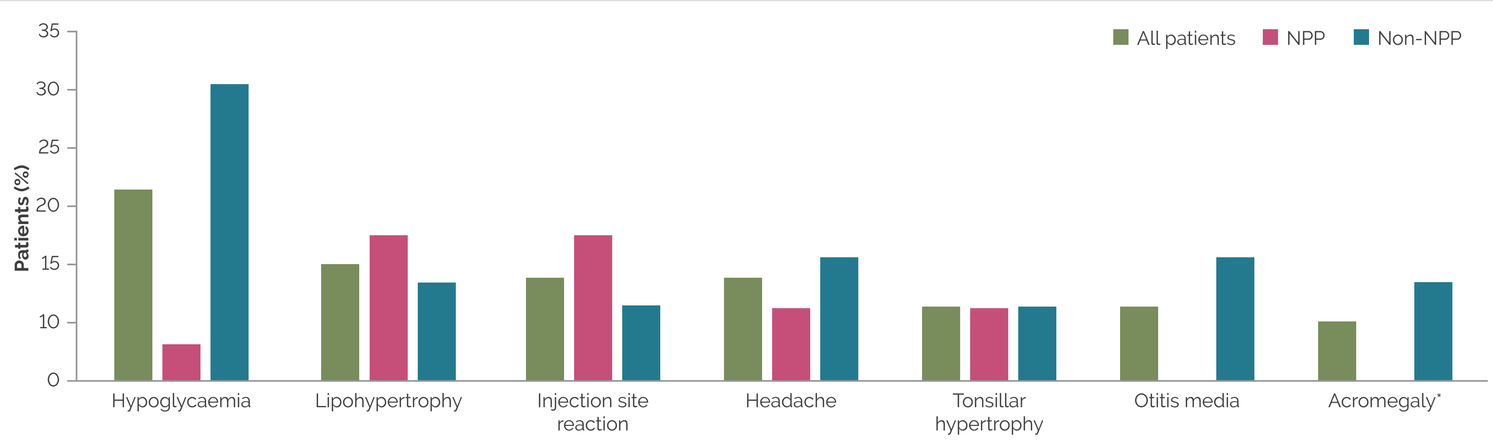
*Includes 1 patient who was undetermined. Data are mean (SD) unless stated otherwise. AE, adverse event; HV, height velocity; GH, growth hormone; NPP, treatment naïve and prepubertal; non-NPP, non-treatment naïve or pubertal; Q, quartile; rhIGF-1, recombinant human insulin-like growth factor-1; SDS, standard deviation score; SPIGFD, severe primary insulin-like growth factor-1 deficiency.

Figure 1. A) Annualised HV and B) height SDS in patients achieving adult height (completer population).



Data are mean (SD). HV, height velocity; NPP, treatment naïve and prepubertal; non-NPP, non-treatment naïve or pubertal; SDS, standard deviation score.

Figure 2. Most common targeted AEs in patients achieving adult height (completer population)



*Acromegalic facial changes were coded as acromegaly. Most common targeted AEs are those reported by ≥5% patients. AE, adverse event.

Treatment

- Median (quartile [Q]1; Q3) treatment duration was 44.3 (27.9; 54.6) months (all patients).
- Median (Q1; Q3) dose was 40.0 (40.0; 50.0) µg/kg twice daily at baseline and 102.3 (85.8; 120.0) µg/kg twice daily during the last year of treatment (all patients).

Effectiveness

- In all patients at year 1:
  - Mean HV (SD) improved (from 4.41 [1.26] to 6.38 [2.53] cm/year [baseline to year 1]) and remained above baseline level for a further 4 years (**Figure 1a**).
  - Mean height SDS (SD) was higher (−3.43) versus baseline (−3.70) and at each year over another 4 years (**Figure 1b**).
- In all patients at final adult height:
  - Height SDS was mean (SD) −3.08 (1.79) (NPP: −2.30 [1.35]; non-NPP: −3.62 [1.88]). Overall, 28.4% (19/67) patients reached a height SDS over −2 (NPP: 44.4% [12/27]; non-NPP: 17.5% [7/40]).
  - The difference between final and baseline height SDS was mean (SD) 0.7 (1.0) (NPP: 1.1 [0.7]; non-NPP: 0.4 [1.0]).
- Within the NPP subgroup:
  - Lower baseline age predicted greater changes from baseline in final adult height SDS (multivariate analysis estimate [95% confidence interval (CI)] by 1-unit increment: 0.25 [0.13; 0.36]; $p<0.001$).

Safety

- In all patients:
  - 14.9% (10/67) reported serious AEs and 6.0% (4/67) reported treatment-related serious AEs.
  - 47.8% (32/67) patients reported targeted AEs. The most frequent targeted AE was hypoglycaemia (NPP: lipohypertrophy and injection site reaction; non-NPP: hypoglycaemia; **Figure 2**).

CONCLUSIONS

- Patients achieving adult height were 12.9 years old at rhIGF-1 treatment initiation. Nevertheless, rhIGF-1 improved adult height in children with SPIGFD, with greater improvements seen in the NPP subgroup than in the non-NPP subgroup.
- Age predicted change from baseline in final adult height SDS in the NPP subgroup.
- Safety is consistent with the known profile of rhIGF-1.

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