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Hypoglycaemic adverse events reported in children enrolled in the European Increlex® Growth Forum Database (EU-IGFD) in Europe (5-year interim data)

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INTRODUCTION

- In the EU, Increlex® (mecasermin [rDNA origin] injection, recombinant human insulin-like growth factor-1 [rhIGF-1]) is approved for the treatment of growth failure in children with severe primary IGF-1 deficiency, which is defined as
  - Height standard deviation score (SDS) ⩽–3
  - IGF-1 <2.5th percentile
  - Normal or elevated growth hormone (GH) secretion
- The EU Increlex® Growth Forum Database (IGFD) Registry was initiated in December 2008 to monitor the safety and efficacy of Increlex® in children, and is representative of the Increlex®-treated patient population in 10 European countries
- The most common adverse event observed with Increlex® is hypoglycaemia, which may be caused by a lack of GH glucoregulatory actions due to severe primary IGF-1 deficiency and further augmented during Increlex® treatment[1,2]
- In clinical trials, hypoglycaemia occurred in up to 49% of children[1,3]
- However, in a real-life setting, data from the EU-IGFD Registry suggest a much lower frequency of 17.6%[2]
- The EU-IGFD Registry is ongoing and recruiting new patients

OBJECTIVES

- EU-IGFD Registry objectives
  - To evaluate the long-term safety (primary objective) and efficacy (secondary objective) of Increlex® in children with growth failure
- Objectives for this poster
  - To report the frequency of hypoglycaemia from 5-year interim data in the EU-IGFD Registry for patients who received at least one Increlex® dose and who attended at least one follow-up visit or for whom there were post-study treatment safety data (safety population)
  - To identify predictive factors for the occurrence of hypoglycaemia
  - To compare first-, second- and third-year height SDSs in all children treated with Increlex® who experienced hypoglycaemia and who had completed at least one follow-up visit (Registry population) with those in children who did not experience a hypoglycaemic event

METHODS

- Ongoing, multicentre, open-label, observational study monitoring the safety and efficacy of Increlex® in children in the clinical practice setting
- Children were eligible for enrolment if they
  - Received Increlex® for growth failure from a qualified practitioner
  - Gave informed consent, if appropriate, in addition to mandatory consent from their parents or legally authorized representative
- Data existing in the patients' medical records as part of standard medical care were collected (using an electronic Case Report Form), including
  - Baseline characteristics
  - Serum IGF-1 concentrations (by local assay providers)
  - Increlex® dose
  - Treatment outcomes, including height
  - Prior use of growth-promoting therapy, including recombinant human GH and rhIGF-1
  - Hypoglycaemia (targeted AE), suspected or documented (blood glucose concentration <50 mg/dL or 2.78 mmol/L)
    - Non-serious hypoglycaemic AEs considered to be treatment related by the treating physician
    - Serious AEs (SAEs) relating to hypoglycaemia irrespective of relationship to treatment*
- Logistic regression analysis was performed to identify predictive factors for the occurrence of at least one hypoglycaemic event in the safety population
  - Covariates in the model: age at first Increlex® dose (years), sex, pubertal group (prepubertal versus pubertal), Increlex® dose at time of hypoglycaemia (µg/kg twice daily [BID]) or mean dose during Year 1 for those without hypoglycaemia, history of hypoglycaemia, prior use of growth-promoting therapy, diagnosis of Laron syndrome, baseline levels of insulin-like growth factor binding protein-3 (IGFBP-3; ng/mL)
  - Variables with a p-value inferior to 0.2 were retained for multivariate analysis
- Time to hypoglycaemia was compared according to mean 1-year Increlex® dose (⩽100 µg/kg BID versus >100 µg/kg BID) using a Gehan test and drawn on a survival curve using the Kaplan–Meier method

RESULTS

Patients

- The first patients were enrolled in the EU-IGFD Registry in December 2008
- 205 patients (132 male; 73 female) were enrolled as of 2 October 2014 (enrolled population)
- 200 patients (130 male; 70 female) were included in the safety population
  - 199 patients (129 male; 70 female) had at least one follow-up visit (Registry population)
  - Post-treatment safety data only were available for 1 patient
- Baseline demographic characteristics are summarized in **Table 1**

HYPOGLYCAEMIA

- Hypoglycaemia (serious and non-serious) was the most common AE with 61 events occurring in 34 patients (17.0% of patients)
  - Of these events, 26 were verified by blood glucose measurement and 27 were suspected; for 8 events the physician did not specify whether they were verified or suspected
  - 5-year data from the EU-IGFD Registry are similar to reports from 3- and 4-year Registry data
  - Of the patients who experienced an event, 19 were male and 15 female
  - Number of hypoglycaemic events per patient per treatment year = 0.11
- Eight hypoglycaemic events in five patients (2.5%) were considered to be serious and of moderate or severe intensity
  - Number of serious hypoglycaemic events per patient per treatment year = 0.01
  - In three patients, hypoglycaemia occurred after fasting or after exercise with no prior intake of food

*Relationship of SAEs to treatment was determined by the treating physician and also reviewed by an expert board.

Table 1. Baseline characteristics of all patients and of those who did or did not experience a hypoglycaemic event (safety population)

	Safety population								
	All patients (N=200)			Patients without a hypoglycaemic event (N=166)			Patients with ⩾1 hypoglycaemic event (N=34)		
Characteristic	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)
Age at first injection, years	200	9.9 (4.0) [9.4; 10.5]	10.5 (6.7, 13.2)	166	10.1 (3.8) [9.5; 10.7]	10.8 (6.7, 13.2)	34	9.1 (4.6) [7.4; 10.7]	8.9 (5.8, 12.9)
Height SDS	190	–3.8 (1.3) [–3.9; –3.6]	–3.4 (–4.5, –2.9)	157	–3.7 (1.3) [–3.9; –3.5]	–3.4 (–4.5, –2.9)	33	–4.0 (1.3) [–4.5; –3.5]	–3.5 (–4.6, –3.0)
IGF-1, ng/mL	170	123.2 (127.6) [103.9; 142.5]	85.8 (44.0, 142.0)	145	124.2 (130.9) [102.7; 145.7]	86.6 (44.5, 142.0)	25	117.4 (108.5) [72.6; 162.2]	83.4 (37.0, 164.0)
Height velocity, cm/year[b]	116	4.8 (1.7) [4.5; 5.1]	4.7 (3.8, 5.7)	95	4.8 (1.8) [4.4; 5.1]	4.7 (3.8, 6.1)	21	4.8 (1.4) [4.2; 5.4]	4.6 (4.0, 5.5)
Prepubertal, n (%)	194	160 (82.5)	N/A	162	132 (81.5)	N/A	32	28 (87.5)	N/A
Diagnosis of Laron syndrome, n (%)	200	29 (14.5)	N/A	166	17 (10.2)	N/A	34	12 (35.3)	N/A
History of hypoglycaemia, n (%)	200	12 (6.0)	N/A	166	8 (4.8)	N/A	34	4 (11.8)	N/A
Prior growth-promoting therapy, n (%)	200	66 (33.0)	N/A	166	53 (31.9)	N/A	34	13 (38.2)	N/A

[a]Number of patients for whom data are available; [b]Enrolled population (N=205).
CI, confidence interval; IGF-1, insulin-like growth factor-1; N/A, not applicable; SD, standard deviation; SDS, standard deviation score.

Predictive factors for hypoglycaemia

- Laron syndrome was a predictor for hypoglycaemia in univariate and multivariate logistic regression analyses (**Table 2**)
- Although patients who experienced a hypoglycaemic event tended to be younger and have a history of hypoglycaemia compared with those who did not experience an event, these factors were not statistically significant

Table 2. Predictive factors for hypoglycaemia (univariate and multivariate analyses)

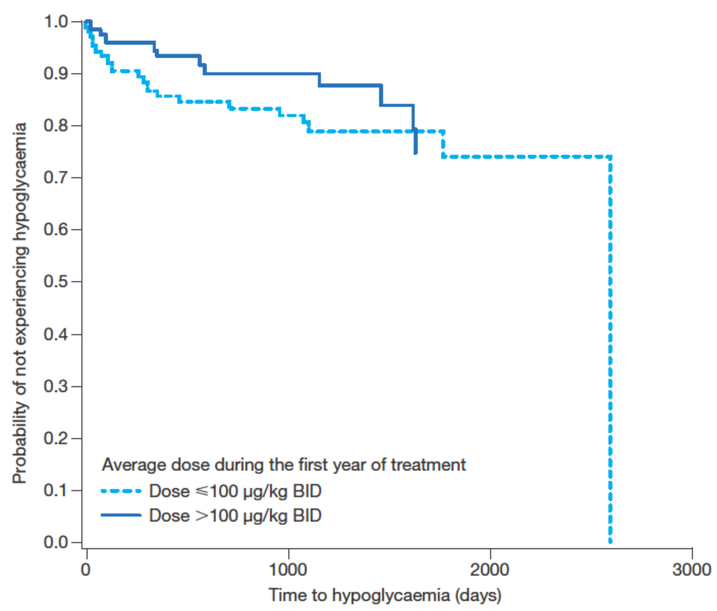
Variable	Odds ratio (95% CI)	p value
Univariate analysis		
Diagnosis of Laron syndrome (yes as reference)	0.21 (0.09; 0.50)	<0.001
Age at first Increlex® dose, years	0.94 (0.85; 1.03)[a]	0.165
Sex (male as reference)	1.59 (0.75; 3.37)	0.223
Pubertal stage (prepubertal as reference)	0.63 (0.21; 1.93)	0.417
Increlex® dose at time of event, µg/kg BID	1.01 (0.99; 1.02)[a]	0.465
History of hypoglycaemia (yes as reference)	0.38 (0.11; 1.34)	0.133
Prior growth-promoting therapy (yes as reference)	0.76 (0.35; 1.63)	0.477
Baseline IGFBP-3, ng/mL	1.00 (1.00; 1.00)[b]	0.776
Multivariate analysis[b]		
Diagnosis of Laron syndrome	0.21 (0.09; 0.5)	<0.001

[a]By 1 unit increment; [b]Factors retained in the multivariate model were history of hypoglycaemia, age at the first Increlex® intake and diagnosis of Laron syndrome.
CI, confidence interval; BID, twice daily; IGFBP-3, insulin-like growth factor binding protein-3.

Increlex® dose and duration of treatment

- At the time of first hypoglycaemic event (serious and non-serious episodes; n=29)
  - Median Increlex® dose was 100 µg/kg BID (95% confidence interval [CI] 80.0; 120.0)
  - Median duration of treatment was 261 days (95% CI 78.0; 353.0)
- In the Registry population, 22 hypoglycaemic events occurred in 105 patients (21.0%) who received an Increlex® dose ⩽100 µg/kg BID and 11 events occurred in 75 patients (14.7%) who received an Increlex® dose >100 µg/kg BID
- A higher Increlex® dose (>100 µg/kg BID versus ⩽100 µg/kg BID) was not clearly associated with the occurrence of hypoglycaemia (**Figure 1**)

Figure 1. Time to hypoglycaemia in patients who received a mean Increlex® dose ⩽100 µg/kg BID versus >100 µg/kg BID (Registry population)



BID, twice daily.
p=0.16 (Gehan test).

Effect of hypoglycaemia on Increlex® effectiveness

- Mean change in height SDS was similar over the first 3 years of receiving Increlex® between patients who did or did not experience hypoglycaemia (**Table 3**)

Table 3. Mean (±SD) height SDS and change from baseline in height SDS in patients who did or did not experience hypoglycaemia (Registry population)

		Height SDS		Change in height SDS
	n[a,b]		n[a]	
Registry population (N=199)				
Baseline	189	–3.74 (1.28)	–	–
Year 1	163	–3.38 (1.31)	156	0.35 (0.47)
Year 2	125	–3.27 (1.45)	119	0.61 (0.65)
Year 3	85	–3.02 (1.62)	80	0.77 (0.69)
Patients without a hypoglycaemic event (N=165)				
Baseline	156	–3.68 (1.27)	–	–
Year 1	134	–3.32 (1.26)	128	0.35 (0.46)
Year 2	100	–3.20 (1.38)	95	0.60 (0.64)
Year 3	66	–2.86 (1.50)	61	0.79 (0.70)
Patients with ⩾1 hypoglycaemic event (N=34)				
Baseline	33	–4.00 (1.30)	–	–
Year 1	29	–3.66 (1.49)	28	0.32 (0.51)
Year 2	25	–3.55 (1.68)	24	0.63 (0.70)
Year 3	19	–3.58 (1.91)	19	0.70 (0.66)

[a]Number of patients for whom data are available; [b]Currently, n ⩽10 for patients with available data from Year 4 onwards (data not shown).
SD, standard deviation; SDS, standard deviation score.

CONCLUSIONS

- In a real-life setting, the proportion of patients treated with Increlex® who experience a hypoglycaemic AE is lower than that previously reported in clinical trials[1,3]
  - Five-year data from the EU-IGFD Registry are similar to reports from 3- and 4-year Registry data[2,4]
- Laron syndrome was identified as an independent predictive factor for the occurrence of hypoglycaemia
- The median Increlex® dose was 100 µg/kg BID at the first hypoglycaemic event
- Age at time of first Increlex® intake and Increlex® dose were not related to hypoglycaemia
- Increlex® effectiveness (change in height SDS) was similar between those who did and those who did not experience hypoglycaemia
- To reduce the potential for hypoglycaemia, Increlex® should be administered in accordance with the product guidance, shortly before or after food[1]

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