Assessment of genetic defects, baseline characteristics and adverse events reported in the Increlex® registry

P2-283

Michel Polak[1], Peter Bang[2], Valérie Perrot[3], Caroline Sert[3], Helen L. Storr[4], Joachim Woelfle[5]

[1]Hôpital Universitaire Necker Enfants Malades, AP-HP, Université de Paris, Paris, France; [2]Faculty of Health Sciences, Linköping University, Linköping, Sweden; [3]Ipsen Pharma, Boulogne-Billancourt, France; [4]William Harvey Research Institute, Queen Mary University of London, London, UK; [5]Children's Hospital, University of Erlangen, Erlangen, Germany

Background

- Certain genetic defects in the growth hormone(GH)/insulin-like growth factor-1 (IGF-1) axis are associated with severe primary IGF-1 deficiency (SPIGFD) and short stature[1,2]
  - For example in the *GHR*, *STAT5B*, *IGF1* and *IGFALS* genes, and in the *GH* gene causing anti-GH antibodies.[3]
- In Europe, SPIGFD is defined as height standard deviation score (SDS) of –3 or less and IGF-1 levels below the 2.5th percentile for age and sex, GH sufficiency and the exclusion of secondary forms of IGF-1 deficiency.[1,4]
- Diagnosis is currently based on clinical and biochemical features; however, the detection of genetic defects may improve the diagnostic journey and clinical management of SPIGFD.
- Mecasermin (Increlex®) is a recombinant human IGF-1 (rhIGF-1) therapy that stimulates linear growth in children with SPIGFD and improves adult height.[4,5]

Objective

To describe the characteristics of children and adolescents with growth deficiency enrolled in the European Increlex® Growth Forum Database (Eu-IGFD; Increlex®) registry according to reported genetic defects.

Methods

- The Eu-IGFD registry is an ongoing, multicentre, open-label, observational study established to monitor the safety and effectiveness of rhIGF-1 therapy in patients with SPIGFD (NCT00903110).[1]
- Patients aged 2–18 years with growth deficiencies, initiating or currently receiving rhIGF-1 therapy and not participating in a clinical trial were eligible for enrolment.
- This complementary analysis describes Baseline characteristics, demographics and reported genetic testing in patients enrolled from December 2008 to 13 May 2019.
- This analysis assessed three subgroups of patients:
  - Those reported to have had genetic testing with ≥1 reported genetic abnormality
  - Those reported to have had genetic testing with no reported genetic abnormalities
  - Those not reported to have had genetic testing.
- Descriptive statistics were used to report the results of genetic tests, patient demographics and characteristics, and safety data. Where applicable, statistical significance was evaluated using the t-test and the Chi-square test.

Table 1. Results of genetic tests in patients with ≥1 detected genetic abnormality in the enrolled population

	Patients with ≥1 reported genetic abnormality (n=56)
GH (with anti-GH antibodies), n	8
Abnormality present, n (%)	7 (87.5)
IGF1, n	5
Abnormality present, n (%)	4 (80.0)
GHR,[a] n	43
Abnormality present, n (%)	42 (97.7)
STAT5B, n	4
Abnormality present, n (%)	2 (50.0)
IGFALS, n	3
Abnormality present, n (%)	1 (33.3)
SHOX, *n*	2
Abnormality present, n (%)	1 (50.0)
PTPN11, n	3
Abnormality present, n (%)	2 (66.7)

Abnormalities in genes "classically" associated with SPIGFD: *GH*, *IGF1*, *GHR*, *STAT5B*, *IGFALS*; abnormalities in genes not "classically" associated with SPIGFD: *SHOX*, *PTPN11*. [a]All patients with a *GHR* abnormality had a diagnosis of Laron syndrome.

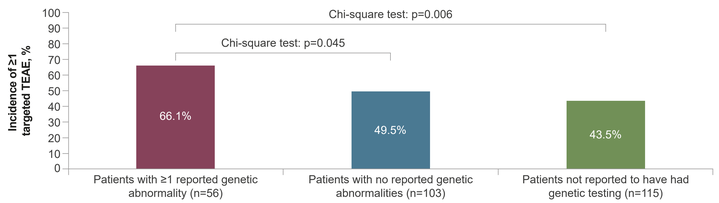
TAKE-HOME MESSAGE

Genetic tests could help to explore some of the causes of short stature; further detection of genetic defects may support the diagnosis of SPIGFD and improve clinical management.

Table 2. Demographics and characteristics of the enrolled population according to genetic test status

	Patients with ≥1 reported genetic abnormality (n=56)	Patients with no reported genetic abnormalities (n=105)	Patients not reported to have had genetic testing (n=117)
Birth length, cm			
n	37	91	99
Mean (SD)	46.1 (4.3)	47.2 (4.1)	49.6 (3.7)
Median (range)	46.5 (33.0, 53.0)	48.0 (26.2, 53.0)	50.0 (38.5, 59.0)
Age at first rhIGF-1 intake			
n	56	105	117
Mean (SD)	9.2 (5.1)	9.0 (4.0)	10.0 (3.7)
Median (range)	8.9 (0, 19)	9.2 (2, 16)	10.2 (3, 17)
Height SDS at first rhIGF-1 intake			
n	48	98	102
Mean (SD)	–4.68 (1.74)	–3.78 (1.17)	–3.37 (1.07)
95% CI	(–5.18, –4.17)	(–4.01, –3.55)	(–3.58, –3.16)
Height velocity prior to first rhIGF-1 intake, cm/year			
n	32	60	57
Mean (SD)	4.9 (1.3)	4.7 (1.8)	4.5 (1.9)
Median (range)	4.9 (1.9, 7.5)	4.6 (1.3, 10.6)	4.5 (0.5, 8.0)
Naïve prepubertal at first rhIGF-1 intake			
n	55	102	113
Yes, n (%)	27 (49.1)	61 (59.8)	73 (64.6)
Reported diagnosis of SPIGFD			
n	56	105	117
Yes, n (%)	51 (91.1)	86 (81.9)	105 (89.7)

Figure 1. Incidence of at least one targeted (serious and non-serious) TEAE according to genetic test status within the safety population



The Safety Population included all patients who received at least one rhIGF-1 injection and had at least one follow-up visit or post-study safety data; 3 patients were excluded as the status of genetic testing was unclear (N=274). Targeted TEAEs were defined in the study protocol.

CONCLUSIONS

- Genetic testing was reported as performed for >50% of patients in the Eu-IGFD registry.
- Patients with reported genetic abnormalities had shorter stature at first rhIGF-1 dose and had more targeted TEAEs than those without reported genetic abnormalities.

Results

Patient enrolment and disposition

- At the time of analysis, 281 patients were enrolled at 118 sites; 3 patients were excluded as the status of genetic testing was unclear (enrolled population: N=278).
- Of the enrolled population, at least one genetic test was performed in 57.9% (161/278) of patients.
- Among those reported to have had genetic testing:
  - ≥1 genetic abnormality was reported in 34.8% (56/161), of whom 96.4% (54/56) had ≥1 genetic abnormality classically associated with SPIGFD (Table 1)
    - Genetic testing of 2/54 patients showed ≥2 abnormalities; mutation/deletion in *GH* and *IGF1* genes and mutation/deletion in *GHR*, *GH* and *SHOX* genes, respectively
  - No genetic abnormalities were reported in 65.2% (105/161).
- A total of 42.1% (117/278) of patients were not reported to have had genetic testing.

Demographics and characteristics

- Patients with ≥1 reported genetic abnormality had lower mean height SDS at first rhIGF-1 intake versus patients without abnormalities (t-test: p=0.002) and those not reported to have had genetic testing (t-test: p<0.001; Table 2).
- No other differences in demographic characteristics were found; notably, the majority of patients were diagnosed with SPIGFD (Table 2).

Safety

- Patients with ≥1 reported genetic abnormality had the highest incidences of targeted treatment-emergent adverse events (TEAEs; Figure 1); the most common targeted TEAE among the three groups was hypoglycaemia (Table 3).
- As of 13 May 2019, 2 cases of serious malignant neoplasms were reported in 2 patients and 6 cases of non-serious benign neoplasms were reported in 6 patients.

Table 3. Targeted (serious and non-serious) TEAEs according to genetic test status within the safety population

	Patients with ≥1 reported genetic abnormality (n=56)	Patients with no reported genetic abnormalities (n=103)	Patients not reported to have had genetic testing (n=115)
Patients presenting ≥1 targeted (serious and non-serious) TEAE, n (%)	37 (66.1)	51 (49.5)	50 (43.5)
Hypoglycaemia, n (%)	20 (35.7)	29 (28.2)	19 (16.5)
Lipohypertrophy, n (%)	9 (16.1)	9 (8.7)	14 (12.2)
Headache, n (%)	8 (14.3)	11 (10.7)	13 (11.3)
General disorders and injection site reactions,[a] n (%)	5 (8.9)	11 (10.7)	9 (7.8)
Tonsillar hypertrophy, n (%)	9 (16.1)	9 (8.7)	7 (6.1)
Otitis media, n (%)	6 (10.7)	8 (7.8)	7 (6.1)
Acromegaly,[b] n (%)	5 (8.9)	1 (1.0)	5 (4.3)
Deafness, n (%)	3 (5.4)	2 (1.9)	3 (2.6)
Sleep apnoea syndrome, n(%)	3 (5.4)	4 (3.9)	0
Myalgia, n (%)	2 (3.6)	1 (1.0)	1 (0.9)
Gynaecomastia, n (%)	1 (1.8)	0	2 (1.7)
Papilloedema, n (%)	0	0	2 (1.7)
Intracranial pressure increased, n (%)	0	1 (1.0)	0
Urticaria, n (%)	0	1 (1.0)	0

All data are reported are correct as of 13 May 2019. The Safety Population included all patients who received at least one rhIGF-1 injection and had at least one follow-up visit or post-study safety data; 3 patients were excluded as the status of genetic testing was unclear (N=274). Targeted TEAEs were defined in the study protocol. [a]Includes oedema and injection site atrophy, bruising, erythema, extravasation, haematoma, hypersensitivity, induration, inflammation, irritation, pain, pruritus, rash, reaction and swelling; [b]Acromegaly refers to acromegalic dysmorphic features.

Abbreviations

cm: centimetre; Eu-IGFD: European Increlex® Growth Forum Database; GH: growth hormone; GHR: growth hormone receptor; IGF-1: insulin like growth factor-1; IGFALS: insulin like growth factor binding protein acid labile subunit; PTPN11: protein tyrosine phosphate non-receptor type 11; rhIGF-1: recombinant human insulin-like growth factor-1; SD: standard deviation; SDS: standard deviation score; SHOX: short stature homeobox gene; SPIGFD: severe primary insulin-like growth factor-1 deficiency; STAT5B: signal transducer and activator of transcription 5B; TEAE: treatment emergent adverse event.

References

1. Bang P et al. Horm Res Paediatr. 2015;83(5):345–57; 2. Storr HL et al. Eur J Endocrinol. 2015;172(2):151–61; 3. Storr HL et al. Endocr Rev. 2019;40(2):476–505; 4. European Medicines Agency, Mecasermin Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/increlex-epar-product-information_en.pdf. Accessed August 2021; 5. Bang P et al. Eur J Endocrinol. 2021;184(2):267–76.

Author contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: MP, PB, JW, HLS, VP, CS; Drafting of the publication, or revising it critically for important intellectual content: MP, PB, JW, HLS, VP, CS; Final approval of the publication: MP, PB, JW, HLS, VP, CS.

Disclosures MP: Research support: Ipsen, Lilly, Merck-Serono, Novo Nordisk, Pfizer, Sandoz, Sanofi; Advisory Boards: Ipsen, Novo Nordisk, Pfizer France; **PB**: Consultancy fees: Ipsen, Lilly, Sanofi, Versatis; **JW**: Research support: Ipsen, Pfizer; Honoraria: Hexal, Ipsen, Merck, Novo Nordisk, Pfizer; Advisory boards: Ferring, Ipsen, Novo Nordisk; **HLS**: Research grants: Merck, Sandoz; Steering group: Novartis; Honoraria: Sandoz; **VP/CS**: Employees of Ipsen.

Acknowledgements The authors thank all patients involved in the study, as well as their caregivers, care team, investigators and research staff in participating institutions.

Medical writing support The authors thank Beatrix Poulton, BSc Hons, of Costello Medical, London, UK for providing medical writing support, and Mark Tassell, BA, of Costello Medical, Cambridge, UK, for design support, which was sponsored by Ipsen in accordance with Good Publication Practice guidelines.

Audio recording The audio accompaniment to this poster was recorded by Peter Bang, with the talking points approved in advance by all co-authors.

This study was sponsored by Ipsen