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Safety of GH in Paediatrics: The GeNeSIS Prospective Observational Study Experience Between 1999 and 2015 (NCT01088412)

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BACKGROUND AND AIMS

Background

- The safety profile of recombinant GH remains good after nearly 30 years (1, 2, 3).
- A general concern regarding the potential influence of GH treatment on neoplasia remains, despite:
  - no increased risk in GH-treated children without cancer history (2, 4, 5, 6)
  - no evidence for increased risk of recurrence, but some evidence for increased risk of second neoplasms in childhood cancer survivors (5,7,8).
- GH is a glucose counter-regulatory hormone that may contribute to insulin resistance (9).
  - Increased type 2 diabetes incidence in GH-treated patients seen in KIGS (10) and GeNeSIS (11).
- Recently French SAGhE findings (in patients with isolated idiopathic GHD, ISS, SGA) indicated increased mortality and risk of haemorrhagic stroke in adults treated with GH as children (12, 13).

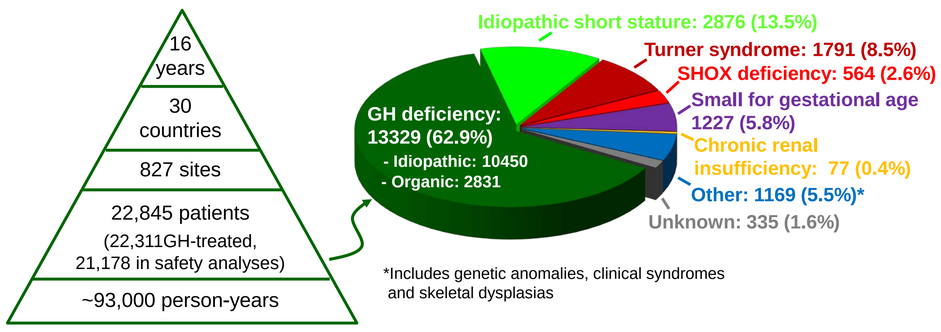
Aims

- To evaluate incidence of key safety outcomes in GH-treated patients who participated in the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) between 1999-2015.
- GeNeSIS was a multinational, prospective observational research program that assessed clinical outcomes of patients treated with GH according to standard paediatric practice.

PATIENTS AND METHODS

Patients

Figure 1: Study enrolment summary and diagnostic groups



- 60% of patients were male.
- Mean ± SD age at study was 10.5 ± 3.8 years; age at first GH dose was 9.6 ± 3.9 y.
- Initial GH dose was 0.27 ± 0.10 mg/kg/wk; duration of follow-up was 4.4 ± 3.2 y.

Statistics

- Standardised mortality (SMR) or incidence (SIR) ratios were calculated using expected cases from general population registries for mortality (14, 15), primary cancer (16, 17) and diabetes (18).
- Person-years (PY) of follow-up were calculated from first to last contacts (later of event onset, last study visit or summary date).
- Exact 2-sided 95% confidence intervals (CI) assumed a Poisson distribution of observed cases.

RESULTS: Neoplasia

Primary Cancers in patients without previous cancer history

Table 1: Primary cancer cases and associated standardised incidence ratio in GH-treated patients

Country[1]	N	PY	Observed cases	Expected cases	SIR (95% CI)	Tumor types
Canada	710	3671	3	1.05	2.87 (0.59–8.38)	Ewing's sarcoma, Osteosarcoma, Neuroendocrine tumour
France	1544	7876	3	2.16	1.39 (0.29–4.07)	Lymphoma, gonadoblastoma, rectal cancer
Germany	2580	14825	5	4.03	1.24 (0.40–2.89)	4 lymphoma, 1 malignant schwannoma
Japan	2230	7302	1	0.99	1.01 (0.03–5.63)	Germinoma
USA	8734	23957	2	6.14	0.33 (0.04–1.18)	Germ cell tumour, malignant naevi
Overall	20146	88749	14	19.62	0.71 (0.39–1.20)	N/A

[Abbreviations: CI = Confidence interval; N/A = not applicable; PY = person-years; SIR = standardised incidence ratio]

[1] Countries with no incident cases are not listed in the table but are included in the overall SIR.

Recurrences and second neoplasms in patients with history of neoplasia.

Table 2: Recurrences and second neoplasms in GH-treated patients

Neoplasm	N	PY	Cases	Patients affected (%)	Crude incidence [per 1000 PY, (95% CI)]
All second neoplasms (SN) in childhood cancer survivors (CCS)	622	2901	34	31 (5.0)	11.7 (8.4–16.4)
All intracranial SN in CCS	622	2901	9	8 (1.3)	3.1 (1.6–6.0)
All recurrences	1087	5151	85	74 (6.8)	16.5 (13.3–20.4)
All intracranial tumour recurrences	823	3964	77	67 (8.1)	19.4 (15.5–24.3)
Craniopharyngioma recurrences	271	1406	42	37 (13.7)	29.9 (22.1–40.4)
Medulloblastoma recurrences	218	1054	9	6 (2.8)	8.5 (4.4–16.4)

[Abbreviations: CI = Confidence interval; PY = person-years

- Of the 31 patients with second neoplasm cases, 24 had history of intracranial tumour (ICT); of the 34 reported second neoplasms, 9 were ICTs
- The most common second neoplasms were meningiomas (4 cases) and osteochondromas (4 cases).

RESULTS continued: Type 2 diabetes

- The SIR (95% CI) for type 2 diabetes for all diagnostic groups was 3.8 (2.2–6.0); the majority of affected patients had risk factors for diabetes (Table 3).

Table 3: Type 2 diabetes and associated standardised incidence ratio overall and by diagnosis group

Diagnosis[1]	N	PY	Observed cases	Expected cases	SIR (95% CI)	Underlying diagnoses and risk factors
All	21448	107101	18	4.8	3.8 (2.2–6.0)	Not applicable
GHD	13507	68526	12	3.1	3.9 (2.0–6.9)	Not applicable
IGHD	10585	49123	4	2.19	1.8 (0.5–4.7)	Obesity [1 patient]
OGHD	2874	19211	8	0.9	9.4 (4.0–18.4)	Leukaemia/irradiation [3], ICT/obesity [2], pre-existing insulin resistance [1]; PWS [1]
TS	1815	10423	3	0.5	6.5 (1.3–18.9)	TS [3]
SGA	1111	5689	2	0.3	7.9 (1.0–28.5)	Russell-Silver syndrome [2]
Other	1488	7491	1	0.3	3.0 (0.1–16.7)	-

[1] Diagnostic groups with no incident cases (ISS, SHOX-D, CRI, UNK) are not listed in the table but are included in the overall SIR.

[Abbreviations: CI = Confidence interval; CRI = chronic renal insufficiency; GHD = growth hormone deficiency; ICT = intracranial tumour; IGHD = idiopathic GHD; ISS = idiopathic short stature; OGHD = organic GHD; PWS = Prader-Willi syndrome; PY = person-years of follow-up; SGA = born small for gestational age; SHOX-D = SHOX deficiency; SIR = standardised incidence ratio; TS = Turner syndrome; UNK = unknown]

RESULTS continued: Mortality and Stroke

- There were 42 deaths in patients with follow-up, giving an overall SMR (95% CI) of 0.6 (0.4–0.8); the only diagnostic group with increased mortality risk was those with organic GHD due to malignancy (Table 4).

Table 4: Deaths and associated standardised mortality ratio overall and by selected diagnosis groups

Diagnosis	N	PY	Observed deaths[a]	Expected deaths	SMR (95% CI)[a]
All	21106	91582	42[b]	69.4	0.6 (0.4–0.8)
GH deficiency (GHD)	13301	57946	28	47.3	0.6 (0.4–0.9)
Idiopathic GHD	10423	42906	3	34.4	0.1 (0.0–0.3)
Organic GHD (OGHD)	2830	14855	24	12.9	1.9 (1.2–2.8)
OGHD - neoplasm	893	4258	16	4.3	3.7 (2.1–6.0)
OGHD – benign neoplasm	285	1445	2	1.6	1.2 (0.2–4.5)
OGHD – malignant neoplasm	530	2504	14[c]	2.4	5.9 (3.2–9.9)
OGHD – non-neoplastic	1937	10597	8	8.5	0.9 (0.4–1.9)
Idiopathic short stature	2663	10488	1	6.6	0.2 (0.0–0.8)
Small for gestational age	1222	5340	2	3.9	0.5 (0.1–1.8)

[Abbreviations: CI = Confidence interval; PY = person-years; SMR = standardised mortality ratio

[a] 11 observed deaths for patients with Turner syndrome, SHOX deficiency, chronic renal insufficiency or other diagnosis, none with significant SMRs

[b] 3 deaths not included in SMR calculation because of no follow-up in study

[c] Deaths in patients with history of malignant neoplasm included 9 recurrences and 2 second neoplasms,

- Patients with haemorrhagic strokes or stokes of unknown type had significant risk factors (Table 5).

Table 5: Cases of and crude incidence of stroke in GH-treated patients

	Cases (%[1])	Crude Incidence[2]	Underlying diagnoses and risk factors
Stroke (all[3])	16 (0.1%)	0.17	Not applicable
Haemorrhagic	3 (0.0%)	0.03	Chronic renal insufficiency/post renal transplant; optic glioma/multiple cerebrovascular disorders; glioma/surgery
Unknown type/ Potential case[4]	3 (0.0%)	0.03	Craniopharyngioma/surgery; medulloblastoma/irradiation/surgery; idiopathic GH deficiency/event term may relate to epilepsy

[1] Percentage of affected patients out of 21,178 at risk [2] Per 1000 person-years [3] Includes 10 ischaemic cases

[4] Cases reported as "cerebral attack", "cerebral subcortical lesion", and "cerebral attacks generalised".

DISCUSSION

- There was no increased risk for all-cause primary cancers in GH-treated patients compared to general population cancer registries, similar to findings from other studies (4, 5).
- The rate of ICT second neoplasms in GeNeSIS was low; aligning with recent data from the Childhood Cancer Survivor Study showing no increased risk for such tumours in GH-treated patients (19).
- Many studies showed no increased risk for ICT recurrences in GH-treated vs non-treated patients (20). The GeNeSIS craniopharyngioma recurrence rate is lower than published rates of 17–36% (21).
- Type 2 diabetes incidence was increased in GH-treated patients, but most had reported risk factors.
- There was no increased mortality risk overall or in any patient group, except for those with history of cancer, aligning with published data from other SAGhE countries (22)
- Similarly, no cases of haemorragic stroke were observed in patients without significant stroke risk factors.
- Limitations associated with the GeNeSIS data include data collection was during GH treatment only, the follow-up per patient was relatively short and low numbers of event cases may hinder interpretation.

CONCLUSIONS

- No new safety signals were observed in *GeNeSIS* in GH-treated patients.
- Compared to general population registries, GH-treated patients in GeNeSIS had:
  - no increased risk for all-cause primary cancers
  - increased risk for type 2 diabetes, but the majority had diabetes risk factors
  - no increased risk of early mortality, except in patients with previous malignancy.
- Safety findings from the French SAGhE cohort were not observed in GeNeSIS,
- Per GH product labelling, glucose monitoring in GH-treated patients with diabetes risk factors is recommended, and patients with ICT/cancer history should be monitored for recurrences and second neoplasms.

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