Long-term safety of growth hormone in adults and adolescents with growth hormone deficiency: An overview of the full cohort in KIMS

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Introduction

- Adult growth hormone deficiency (GHD) is associated with abnormal body composition, reduced bone mineral density, decreased physical capacity, unfavourable metabolic profile, and impaired quality of life[1,2]
  - Untreated patients may have decreased life expectancy due to cardiovascular and cerebrovascular diseases[3,4]
- GH replacement in patients with GHD has beneficial effects on lean and fat body mass,[5,6] bone health,[7,8] lipids,[6,9,10] and quality of life[11]
- Long-term GH therapy in adults with GHD is overall well-tolerated,[12,13] but concerns of potential risk for diabetes, new malignancy, tumour recurrence, and cardiovascular diseases still remain
- KIMS (Pfizer International Metabolic Database; initiated December 1993; closed October 2012) was an international, multicentre, observational, open-label database of long-term clinical and safety outcomes of GH (Genotropin® [somatropin]; Pfizer, New York) in adult and adolescent hypopituitary patients with GHD, as prescribed in routine clinical practice

Objective

- To evaluate the overall safety outcomes of the full cohort of GH-treated patients in KIMS until database close

Methods

- Hypopituitary adults and adolescents with confirmed GHD and closed epiphyses who were prescribed GH (Genotropin® [somatropin]; Pfizer, New York) were enroled
- Safety outcomes included all reported adverse events (AEs) and serious AEs (SAEs) regardless of causality
- Treatment outcomes included clinical characteristics (e.g., height, weight, blood pressure [BP], waist and hip circumferences, insulin-like growth factor-1 [IGF-1], lipid profile)

Results

Patient Characteristics

- The full GH-treated cohort included 15,809 patients from 31 countries, with mean follow up of 5.3 years (maximum 18.3 years; total 83,128.3 patient-years)
- Mean age of patients at KIMS start was 44 years; the majority were Caucasian (94%) and approximately half were male (51%)
- The majority of patients had adult-onset GHD (77%). Most patients had pituitary/hypothalamic tumours (60%) as the cause of GHD, while 22% had idiopathic/ congenital GHD, and 18% had other aetiologies
- Mean±SD dose of GH prescribed at baseline was 0.30±0.3 mg/day for males and 0.30±0.29 mg/day for females, increased to 0.39±0.28 mg/day and 0.44±0.30 mg/day, respectively, at year 1, and remained almost constant during follow up

Adverse Events

- AEs were reported in 51.2% of patients (treatment-related in 18.8%) and SAEs in 25.3% of patients (treatment-related in 4.3%) (**Table 1**)
- Arthralgia and peripheral oedema were the two most frequently reported AEs; the most frequently reported SAE was pituitary tumour recurrence (**Table 1**)
- Of 387 patients who discontinued GH treatment due to treatment-related SAEs, the most frequent causes were pituitary tumour recurrence (15.2% [59/387]), recurrence or worsening of craniopharyngioma (4.7% [18/387]), and prostate cancer (4.4% [17/387])
- AE and SAE incidence rates were affected by baseline age, GHD onset, prior pituitary radiation, and mean IGF-1 standard deviation score (SDS). Rates were higher in patients with pituitary/hypothalamic tumour versus idiopathic/congenital aetiologies, and with lower versus higher mean daily GH dose prescribed in KIMS. (**Table 2**)

Table 1. Commonly reported AEs and SAEs (N=15,809)

Number of patients	All causality, n (%)	Treatment-related, n (%)
Patients with ≥1 AE	8093 (51.2)	2979 (18.8)
Patients with ≥1 SAE	3998 (25.3)	680 (4.3)
AEs occurring in ≥2% patients (by MedDRA PT)		
Arthralgia	730 (4.6)	407 (2.6)
Peripheral oedema[a]	612 (3.9)	485 (3.1)
Headache	572 (3.6)	156 (1.0)
Influenza	450 (2.8)	3 (0)
Depression	447 (2.8)	35 (0.2)
Pituitary tumour recurrence	424 (2.7)	200 (1.3)
Back pain	387 (2.4)	29 (0.2)
Nasopharyngitis	330 (2.1)	3 (0)
Fatigue	322 (2.0)	78 (0.5)
SAEs occurring in ≥0.5% patients (by MedDRA PT)		
Pituitary tumour recurrence	320 (2.0)	154 (1.0)
Death	143 (0.9)	21 (0.1)
Pneumonia	148 (0.9)	2 (0)
Cerebrovascular accident	122 (0.8)	5 (0)
Gastroenteritis	114 (0.7)	1 (0)
Myocardial infarction	81 (0.5)	2 (0)
Craniopharyngioma	81 (0.5)	33 (0.2)
Prostate cancer	81 (0.5)	28 (0.2)
Neoplasm recurrence	77 (0.5)	42 (0.3)

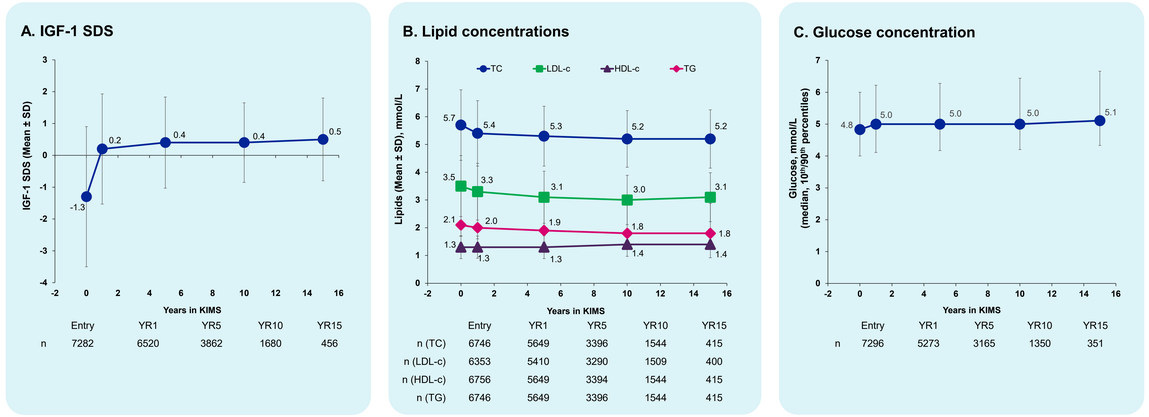
AE, adverse event; IGF-1, insulin-like growth factor 1; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event.
[a]Fluid retention and oedema peripheral MedDRA PTs combined; patients counted once for the combined term.

Table 2. Observed crude rate (per 1000 PY) of AEs and SAEs by patient characteristics

Characteristic	PY	AEs		SAEs	
		Any	Related	Any	Related
Age at KIMS start, years					
≤29	18,695	234.4	32.1	53.0	4.6
30–44	24,477	326.6	53.4	66.3	6.4
≥45	39,956	381.8	58.6	104.3	10.7
P		0.0141	0.0313	0.3052	0.0664
GHD aetiology					
Idio/Cong	13,457	253.6	48.1	47.5	3.8
Pit/Hyp	55,162	355.0	53.4	91.4	9.9
Other	14,273	320.3	45.5	75.9	5.0
P		<0.0001	0.0014	0.2567	0.9400
GHD onset					
CO	21,063	257.9	39.3	54.3	4.5
AO	61,977	357.9	55.2	90.9	9.3
P		<0.0001	0.0008	0.0345	0.3437
Prior pituitary radiation at KIMS start					
No	29,737	347.7	55.2	96.2	11.7
Yes	25,697	361.1	50.0	86.5	7.7
P		<0.0001	0.0004	<0.0001	0.2971
IGF-1 SDS[a]					
≤0	26,958	317.8	57.3	83.5	8.6
>0	38,515	351.0	45.6	87.0	8.0
P		<0.0001	<0.0001	<0.0001	0.0054
Daily GH dose[b]					
≤0.30 mg	29,622	358.9	62.0	99.2	11.4
>0.30 mg	53,507	317.7	45.1	71.8	6.2
P		<0.0001	<0.0001	<0.0001	0.0709

P-value: at least one rate is different from the others in the comparison. AE, adverse event; AO, adult-onset; CO, childhood-onset; GH, growth hormone; GHD, growth hormone deficiency; Idio/Cong, idiopathic/congenital aetiology; IGF-1, insulin-like growth factor 1; Obs, observed number of cases; Pit/Hyp, pituitary/hypothalamic tumour; PY, patient-years; SDS, standard deviation score.
[a]Based on mean IGF-1 SDS during KIMS from first to last visit. [b]Based on mean GH doses per day during KIMS from first to last visit.

Figure 1. Evolution of (A) IGF-1 SDS, (B) centrally measured serum lipid variables and (C) concentrations of fasting blood glucose during KIMS follow up



	Entry	YR1	YR5	YR10	YR15
n	7282	6520	3862	1680	456

	Entry	YR1	YR5	YR10	YR15
n (TC)	6746	5649	3396	1544	415
n (LDL-c)	6353	5410	3290	1509	400
n (HDL-c)	6756	5649	3394	1544	415
n (TG)	6746	5649	3396	1544	415

	Entry	YR1	YR5	YR10	YR15
n	7296	5273	3165	1350	351

Mortality

- A total of 606 deaths (3.8% of patients) were reported in KIMS; the most common causes were neoplasms (n=146), cardiac or vascular disorders (n=71), infections/infestations (n=60), and cerebrovascular disorders (n=48); causes of death were available for 560 patients

De Novo Cancer

- *De novo* all-site cancer incidence (in those without prior cancer history) was comparable to that of the general population[14] in the full cohort, or in subgroups defined by gender, GHD onset, prior GH treatment status, prior irradiation at KIMS start, time interval in KIMS follow up, or mean GH dose
- Standard incidence ratios (SIRs; 95% CI) of *de novo* cancer versus the general population were lower in patients with idiopathic/congenital GHD (0.64; 0.43−0.91), but were not significantly affected in patients with pituitary/ hypothalamic tumours (0.96; 0.87−1.07) or other aetiologies (0.80; 0.56−1.10)
- SIRs were elevated in younger patients who aged 15−24 years at baseline (2.25; 1.08−4.13) or attained age 25−29 (2.90; 1.16−5.97) or 30−34 (2.78; 1.39−4.97) in KIMS
- Mean IGF-1 SDS ≤0 was associated with a higher SIR (1.32; 95% CI 1.11−1.55), and mean IGF-1 SDS >0 with a lower SIR (0.77; 95% CI 0.67−0.89)
- Risks for prostate (1.21; 0.97−1.50), breast (0.56; 0.40−0.77), or colon (0.66; 0.41−1.01) cancers were not higher than in the general population

IGF-1 Level, Lipid Profile and Glucose Metabolism

- Mean±SD IGF-1 SDS increased from -1.3±2.2 at baseline to +0.2±1.7 at year 1, and reached +0.5±1.3 at year 15 (**Figure 1A**)
- Effects of GH on lipids and fasting blood glucose concentration were neutral (**Figure 1B-C**)

Conclusions

- In the present analysis of the full GH-treated cohort of KIMS, one of the largest and longest real-world safety surveys, GH replacement was safe and tolerable as currently prescribed in routine clinical practice, with no new safety signals observed
- *De novo* cancer risk was not higher in KIMS GH-treated patients versus the general population. A decreased SIR was found in patients with idiopathic/congenital GHD, but not pituitary/hypothalamic tumours, suggesting that factors related to hypopituitarism or primary pituitary disease may have contributed to the cancer incidence in the full cohort
- Mean IGF-1 SDS during follow up appeared to be inversely related to the overall *de novo* cancer risk and the risk of colon cancer was not increased in the KIMS cohort, in contrast to epidemiological data and acromegaly studies that suggested increased cancer risk with high serum IGF-1 levels[15]
- Impacts of GH replacement on lipids and glucose metabolism were neutral
- Data from KIMS are complementary to those from randomized clinical trials and reinforce the favourable safety profile of long-term GH replacement in adults with GHD

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