Poster P2–176 Abstract No. 344

Efficacy and Safety of Growth Hormone (GH) in the Treatment of Children with Hypochondroplasia (HCH): Comparison with a Historical Cohort of Untreated Children with HCH

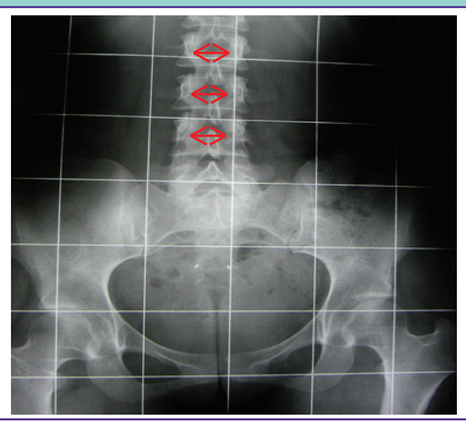
Graziella Pinto[1], Dinane Samara-Boustani[1], Magali Viaud[1], Valérie Cormier-Daire[2], Yeriley Lopez[3], Laurence Fresneau[3], Marie Piketty[4], Jean Claude Pineau[5], Michel Polak1,[6]

[1]AP-HP, Hôpital Universitaire Necker Enfants Malades, Pediatric Endocrinology and Diabetes, Paris, France; [2]IMAGINE institute, Medical Genetics Department; [3]Merck,sas, Lyon, France; [4]AP-HP Hôpital Universitaire Necker Enfants Malades, Physiology Laboratory; [5]CNRS FRE 2029, Paris; [6]Université Paris Descartes

INTRODUCTION

- Hypochondroplasia (OMIM146000) is a skeletal dysplasia, inherited as an autosomal dominant trait, mainly caused by mutations in the Fibroblast Growth Factor Receptor 3 (FGFR3) gene, expressed in the growth plates of long bones during endochondral ossification and characterized by disproportionate short stature (fig.1).
- The importance of growth defect is variable and due in part to an inadequate pubertal growth spurt. Appan and al. reported final heights between 145-165 cm in boys and 133-151 cm in girls and Maroteaux mean final height 146.1 ± 4.9 cm in boys and 137.6 ± 6.3 in girls.
- Treatment of HCH with growth hormone (GH) has been reported with study limitations due to short treatment period.

Fig 1. X-ray in a patient with HCH: failure of increase in the interpedicular distance from the 1st to the 5 th lumbar spine is the almost constant criterion. Short and broad femoral necks



AIMS

- To determine the efficacy of GH therapy on the height (SDS) in children with HCH treated during at least 5 years in comparison with a historical cohort of 40 non-treated HCH subjects
- To study the baseline to 5-year changes on the height, growth velocity, body proportions (upper segment, head circumference, body mass index (BMI), body composition (percent total fat mass, lean body mass, bone mineral density).
- To assess the correlation of genotype at baseline with phenotype of treated patients.

METHODS

Historical cohort

- An historical cohort was identified from patients followed by pediatricians at the Bone Dysplasia Center at Necker Enfants-Malades Hospital. It was composed of 40 patients (22 boys, 18 girls) with HCH, and with height and weight data available from 3 years of age until final height. Growth charts were modeled after these data and height SDS were calculated. A model to predict the growth and final height of patients without growth hormone (GH) therapy was designed.

Study

- The HCH subjects were diagnosed on specific skeletal abnormalities and confirmed by 2 experienced physicians of the Bone Dysplasia Center at Necker Hospital. Inclusion criteria were : chronological age ≥3 yrs, bone age ≤11yrs for girls and ≤13 yrs for boys, initial height -2SDS, analysis of FGFR3 gene known, written informed consent from parents.
- 19 patients (9 males, 10 females) were included in the study independently of FGFR3 gene results.
- **8** patients treated **during at least 5 years** allowed to make a longitudinal analysis. 4 males, 4 females at a mean age of 6,8 ± 2,6 years (range 3,3-10,9 yrs) were treated with r-GH (Saizen®, Merck France) at an initial dose of **0.057** mg/kg/day (dose adjusted with IGF-I levels)

RESULTS

- After 5 years of treatment, height gain was **+0,89 (± 0,60) SDS** obtained essentially during the first year of treatment but it was **+1,57 (± 0,8 SDS)** i,e. 7,5 cm compared to a historical cohort of non-treated HCH (fig1).
- Body proportions measured by sitting height to standing height ratio SDS score shows initial high values that increased moderately and not significantly (Table1).

Table1. Clinical, biological and radiological parameters at baseline and after 1,2,3 and 5 years of r-GH treatment

	Baseline	1st yr	2nd yr	3rd yr	5th yr	Total gain during 5 yrs treatment Mean (95% ICs)
Height velocity (cm)		8.6±1.3	6.8±1.5	5.3±3.1	4.4±1.45	
Height (SDS)/Sempe[1]	-2.44	-1.91**	-1.47**	-1.42**	-1.55	**+0.89*** (0.4;1.4)
BMI (SDS)/Sempe[1]	1.24	1.11	1.28	1.52	1.00	-0.24 (-1.4;0.9)
Height/HCH[2] (SDS)	0.53	1.32**	1.91**	2.12**	2.10**	**+1.57*** (0.9;2.2)
Upper segment/height (SDS)	4.1	4.1	3.9	4.8	4.5	+0.68 (-1.7; 3.0)
Head circumference[1] (SDS)	2.47	2.82	2.34	2.00	2.25	+0.55 (-0.1;1.2)
% Total fat mass[3] (SDS)	1.33	0.3	0.22	0.18	0.52	-0.81 (-1.8;0.03)
BMD[3] (Zscore)	-1.70	-1.76	-1.53	-1.67	-1.74	-0.32 (-1.3;0.9)
IGF-1[4] (Zscore)	-0.76	1.47	1.74	1.69	1.48	

*p<0,05 **p<0,01
[1]values in SDS of Standard French population published by Sempé; [2]values in SDS of non-treated historical cohort of patients with HCH; [3]Body composition and lumbar spinal mineralometry evaluated by dual X ray absorptiometry; [4]IGF1 values at M0, M12, M24, M36, M60

- BMI and % fat mass didn't change significantly.
- There was a difference in response between patients with FGFR3 mutation (n=5) versus the others. Height gain was respectively + 0,6 (± 0,5) SDS vs +1,4 (± 0,2) SDS.
- Correlation in height gain was observed between the first and the fifth year (r=0,78, p<0,05) (fig2). A height gain > +0,5 DS after 1 year of treatment is predictive of a good response after 5 years.
- No treatment related serious adverse events were reported.

Fig 2. Evolution of height in patients with HCH treated by GH during 5 years. Height is expressed in SDS of Standard French population published by Sempé (red rectangle) and in SDS compared to a non-treated historical cohort of patients with HCH (blue rectangle)

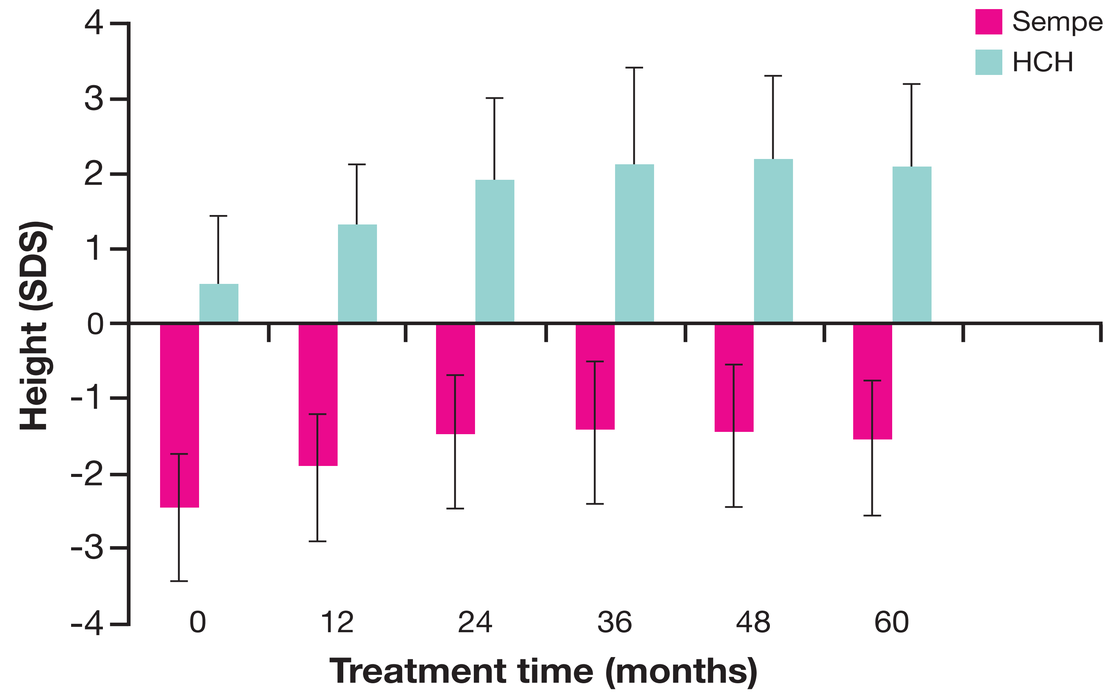
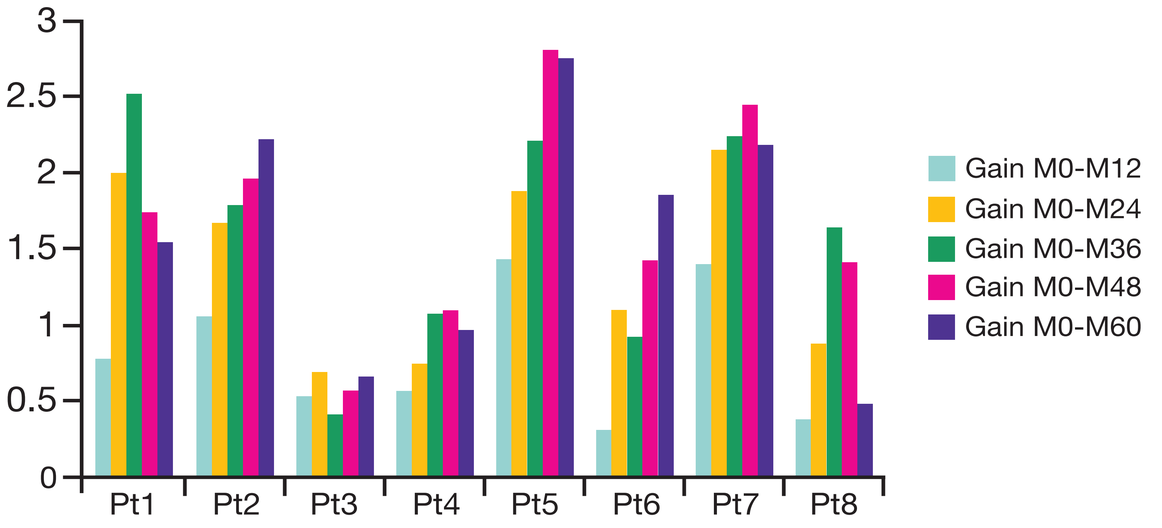


Fig 3. For each patient evolution of annual height gain expressed in SDS compared to a non-treated historical cohort of patients with HCH



CONCLUSIONS

- **GH is effective in improving growth in some patients particularly HCH without FRFR3 mutation.**
- **Response during the first year is predictive of final response and could be used to decide to continue treatment until final height.**
- **GH therapy was well tolerated.**

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ACKNOWLEDGMENTS

This study was sponsored by Merck France

DISCLOSURES

GP, JCP, DSB, MP have received honoraria from Merck for their contribution to the study. YL and LF are employees of Merck France

Centre de Référence des Maladies Endocriniennes Rares de la Croissance

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FACULTÉ DE MÉDECINE PARIS DESCARTES

Presented at ESPE 2019, 19-21 September, 2019; Vienna, Austria

58ESPE P2-176

Growth and syndromes (to include Turner syndrome)

Graziella Pinto

Poster presented at: ESPE 2019 VIENNA

PosterSessionOnline.com