Determinants of final height in patients born small for gestational age treated with recombinant growth hormone (rhGH).

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INTRODUCTION

About 15% of children born small for gestational age (SGA) do not reach final height within normal range.

Recombinant human growth Hormone (rhGH) has shown to be effective in catching up growth velocity and height in children born SGA.

OBJECTIVE

Identify the predictive factors of final height in children born SGA treated with rhGH.

MATERIAL & METHODS

Study:

- Monocentric.
- Retrospective.
- In a tertiary pediatric endocrinology referral center.

Patients :

- Age > 16 years
- Born SGA defined as birth length or weight <10th centile.
- Final height (FH) available.
- Treated with rhGH for more than one year.
- Treated or not treated with GnRH analogues (GnRHa).
- Patients treated with aromatase inhibitors were excluded.

RESULTS

255 patients were included in this analysis (table 1).

Birth length: -2.0 (±0.7) SD.
Height at onset of rhGH: -2.2 (±0.9) SD.

Duration of rhGH treatment : 4.5 (±2.8) years.
120 patients received GnRH analogues.

During treatment the height increased from -2.2 (±0.9) SD to -1.2 (± 0.8) SD.
The final height was : to -1.5 (± 0.9) SD.

The Figure 1 shows the evolution of height SD of the whole cohort from birth until FH.

Table 1: Clinical Characteristics of the 255 SGA patients treated with rhGH
Values are provided as mean ± SD

	Girls	Boys	P value
Number of patients	157	98	
Term (weeks of amenorrhea)	38 ± 2.8	37.9 ± 2.8	0.22
Birth length (SD)	-1.9 ± 0.7	-2.2 ± 0.7	0.05
Birth weight (SD)	-1.6 ± 1	-1.9 ± 1	0.03
Target height (SD)	-0.8 ± 0.7	-0.7 ± 0.8	0.3
Growth velocity before rhGH (cm/yr)	5.3 ± 1.6	4.7 ± 1.1	0.003
Age at onset of rhGH (yrs)	10 ± 2.4	9.7 ± 3.4	0.07
Height at start of rhGH (SD)	-2.1 ± 1	-2.4 ± 0.7	0.007
IGF-1 at start of rhGH (SD)	-0.9 ± 0.9	-1.1 ± 0.8	0.3
Bone age-chronological age difference at onset of rhGH (yrs)	-0.7 ± 1.2	-1.6 ± 1.2	<0.0001
Age at onset of puberty (yrs)	11 ± 1.3	13 ± 1.3	<0.0001
Height at onset of puberty (SD)	-1.6 ± 0.8	-1.5 ± 0.9	0.25
Height at menarche (SD)	-1.2 ± 0.9	Not applicable	Not applicable
Final height (SD)	-1.5 ± 0.9	-1.4 ± 1	0.28
Dose of rhGH during the 1st year (ug/kg/day)	71 ± 20	65 ± 18	0.019
rhGH alone / rhGH and GnRH analogues	67/90	68/30	<0.0001
Number of years of rhGH treatment	3.8 ± 2.3	5.7 ± 3.2	<0.0001

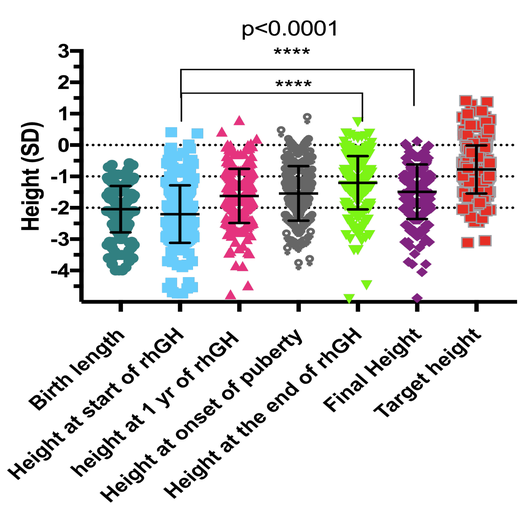

Figure 1 : Mean (± SD) height of 255 patients at birth, at start of rhGH, at onset of puberty and final height compared to the target height.
Height at start of rhGH vs Final height (p<0,0001).
Height at start of rhGH vs height at the end of rhGH (p<0,0001).

RESULTS

Multivariate analysis (table 2)

We identified 8 factors that predict 46 % of the final height in this cohort.

- SGA causes.
- Treatment with GnRHa > 2 years.
- Birth length.
- Height at start of rhGH
- IGF1 at start of rhGH treatment.
- Growth velocity during the first year of treatment.
- Age at onset of puberty.
- Height at onset of puberty.

Table 2: Predictive factors of final height in 191* patients born SGA treated with rhGH using multiple regression analysis

Variable	Coefficient	P value	Partial R^2
Groups of treatment			
-GH alone	Ref.	Ref.	<0.1%
-GH + GnRH analogues <2 yrs	0.26	0.03	
-GH + GnRH analogues ≥2 yrs	0.42	0.006	
Cause of SGA			
-SGA no catch up	Ref.	Ref.	10%`
-Chromosomic abnormalities or bone malformations	-0.62	<0.0001	
-Placenta insufficiency or pre- eclampsia	-0.23	0.23	
-Other	-0.17	0.28	
Birth length (SD)	0.16	0.02	4%
Height at start of rhGH (SD)	0.40	<0.0001	5%
IGF1 at start of rhGH (SD)	-0.26	0.0002	10%
Growth velocity at 1 yr of rhGH (cm/year)	0.09	0.0002	8%
Age at onset of puberty (yrs)	0.19	<0.0001	5%
Height at onset of puberty (SD)	0.25	0.0007	4%
R^2	0.46		

*64 patients were excluded because bone age at start of rhGH was non-included in the model (missing data)

Response to rhGh (table 3)

The better response was associated to

- Absence of chromosomic abnormalities or bone malformations.
- Mother's height -height between -1 SD and 0 SD.
- A great growth velocity at one year of treatment.
- An extended time on treatment.
- A low IGF1 at initiation.
- A late pubertal development.
- A short stature at onset of puberty.

Table 3 : Predictive factors of rhGH'response

	Bad responders N=57	Medium responders N=111	Good responders N=87	MULTIVARIATE OR [IC95%]	p
Cause of SGA n (%)					
-SGA no catch up	34 (60%)	71 (64%)	64 (74%)	Ref.	
-Chromosomic abnormalities or bone malformations	13 (23%)	15 (13%)	7 (8%)	0.1 [0.05-0.4]	0.0003
-Placenta insufficiency or pre-eclampsia	3 (5%)	13 (12%)	5 (6%)	0.1 [0.03-0.4]	
-Other	7 (12%)	12 (11%)	11 (13%)	0.4 [0.2-1.2]	
MH, n (%)					
<-1.5 SD	15 (26%)	26 (23%)	22 (25%)	Ref.	
-1.5 à -1 SD	11 (19%)	18 (16%)	9 (10%)	0.6 [0.2-1.7]	0.02
-1 à -0 SD	15 (26%)	46 (41%)	40 (46%)	2.5 [1.02-5.9]	
≥ 0 SD	16 (28%)	21 (19%)	16 (18%)	1.4 [0.5-4.0]	
GV at 1 year of rhGH, mean (cm)	6.8 (2.2)	8.7 (1.9)	9.5 (1.8)	1.3 [1.1-1.6]	0.004
Numbers of **years of rhGH treatment** mean (years)	3.0 (2.5)	4.4 (2.5)	5.6 (2.9)	1.6 [1.3-1.9]	<0.0001
IGF1 at start of rhGH, mean (SD)	-0.2 (0.9)	-1.1 (0.6)	-1.4 (0.6)	0.4 [0.2-0.6]	<0.0001
Age at onset of puberty, mean (year)	10.4 (1.4)	11.6 (1.4)	12.1 (1.5)	1.9 [1.4-2.5]	<0.0001
Height at onset of puberty (SD)	-1.3 (0.9)	-1.6 (0.7)	-1.6 (1.0)	0.6 [0.4-0.9]	0.03

Safety results (figure 2)

IGF1 increased from -1 SD (± 0,8), to 0.4 SD (± 1.2) after one year, until 0.8 SD (± 1) at the end of rhGH. It remained in the target range.

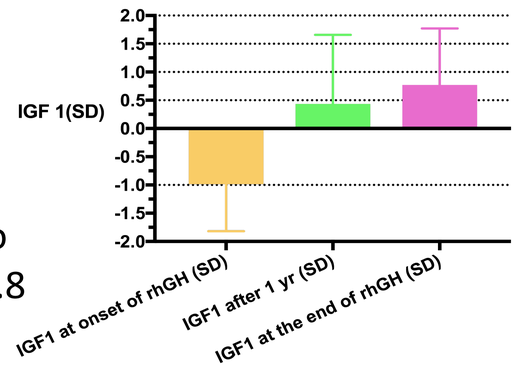

Figure 2 : Serum value of IGF1 (SD) at onset, after 1 yr and at the end of rhGH

CONCLUSION

In this large cohort of patients who achieved their growth we were able to identify several factors influencing the final height and the response to growth hormone therapy in children born SGA.
Our results confirme that the efficiency of rhGH is associated with the duration of treatment and the timing of puberty. They are concordant with the study of Van Pareren and al.*(Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. J Clin Endocrinol Metab. août 2003)*

This will likely help the management of rhGH in the future for this specific target population.

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