The Effect of Longterm Growth Hormone Treatment in Children with Short Stature Secondary to Intrauterine Growth Retardation

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The great majority of children born with intrauterine growth retardation (IUGR) has spontaneous catch up growth during the first 2 years of life. This proportion exceeded 80% in the large cohort of Swedish newborns recently collected by Karger et Albertsson-Wikland (1). In the absence of this initial catch up growth, the persistence of prepubertal short stature leads to a reduced adult height (2, 3). In a personal series of 47 children born with IUGR and seen before puberty for growth retardation below -2 SDS, the mean adult heights were respectively 161.9 ± 8.0 cm in males and 147.6 ± 7.2 in females, values highly significantly lower than the target heights of these patients (4). In addition, 21% of the short stature adult population is represented by subjects born with IUGR (1). This reduction in both prepubertal and adult height, indicates the possible usefulness of GH therapy in short children born with IUGR. The aim of the present report is to summarize the results of 3 multicenter French studies using various doses of GH during 3 years in relatively large series of short children born with IUGR. Additionally a post treatment follow up of 1 year was analyzed in 2 of these trials.

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Materials and Methods

216 prepubertal children with short stature below 2 SDS born with heights inferior to -2 SDS according to the standards established by Usher and MacLean (5) were enrolled in 3 French protocols of GH therapy. All these children had normal GH secretion on at least one pharmacological stimulation test, normal skeleton X rays and in girls, a normal karyotype. Patients with great prematurity (< 35 weeks of gestation) or documented syndromes, including Silver Russel, were excluded from these protocols. The mean characteristics of the patients included are given in Table 1.

The 3 protocols varied in the age of the enrolled children, the dose and brand of GH.

Trial 1 included 130 children with ages ranging between 4 and 8 years. The patients were randomized between a non placebo control group and 2 GH doses: 0.7 and 1.4 U/kg/week. GH used in this study was Genotonorm (Pharmacia). Data at 2 years have been previously published (6).

Trial 2 included 55 children with ages ranging between 4 and 11 years in boys, 4 and 10 years in girls. The patients were randomized between 2 doses: 0.4 and 1.2 U/kg/week. GH

Table 1 Characteristics of patients included in 3 French trials

Trial	Gestation (weeks)	Birth height (cm)	Birth weight (g)	Father's height (cm)	Mother's height (cm)
1	39 ± 1.8	43.6 ± 2.8	2,200 ± 500	170 ± 6	157 ± 5
2	39.1 ± 1.6	43.6 ± 2.6	2,145 ± 520	171 ± 5	157 ± 6
3	37.8 ± 2.9	42.7 ± 3.7	2,031 ± 551	170 ± 7	157 ± 8

Table 2 Baseline characteristics of patients included in 3 French trials

	N	Dose (U/kg/w)	Age (years)	Height (SDS)	Bone Age (Years)	Growth velocity (cm/year)
Trial 1	27	0	4.3 ± 1.4	-2.8 ± 0.5	3.9 ± 1.3	5.2 ± 0.9
(Genotonorm)	55	0.7	5.3 ± 1.4	-3.0 ± 0.8	4.0 ± 1.3	5.1 ± 0.5
	48	1.4	5.7 ± 1.3	-2.9 ± 0.8	4.8 ± 1.4	4.7 ± 0.9
Trial 2	15	0.4	8.4 ± 0.6	-3.1 ± 0.2	6.9 ± 0.7	5.8 ± 0.5
(Maxomat)	40	1.2	8.1 ± 0.3	-3.2 ± 0.1	6.9 ± 0.3	4.8 ± 0.6
Trial 3	31	1.4	4.8 ± 1.8	-3.3 ± 0.6	3.5 ± 1.7	5.5 ± 2.0
(Saizen)						

used in this study was Maxomat (Sanofi). Data at 2 and 4 years have been previously published (7, 8).

Trial 3 concerned 31 children aged 2 to 8 years, treated with a single dose of GH: 1.4 U/kg/week. GH used in this study was Saizen (Serono).

Baseline characteristics of patients included in these 3 trials are given in Table 2.

In the 3 trials growth hormone was administered for 3 years in daily subcutaneous injections. An additional follow up of 1 year is available in trials 1 and 2. In trial 1 at the end of the 3rd year, patients were randomized between interruption of GH and continuation for an additional year. In trial 2, GH was interrupted in all the children.

Results

Effects of the 3 years of GH therapy

As shown on Table 3, GH therapy induced a catch up growth ranging between + 0.7 and +

2.0 SDS, variable with the dose. This dose effect relationship is illustrated on Fig, 1. A spontaneous catch up growth of 0.7 SDS was observed in the control group. The rate of bone maturation was accelerated in all groups of patients, including in the control group, without any relationship with the dose (Table 3).

Post treatment year

The evolution of height in SDS during the 4th year without treatment (trials 1 and 2), or with an additional year of GH therapy (trial 1) is shown in Tables 4 and 5.

Puberty

Puberty started in 34 patients of trial 2 during the 3rd year on GH, and in 10 others during the 4th year (off GH). The mean chronological age at the onset of puberty was 12.6 years in boys, 11.0 years in girls, with mean bone ages of 11.3 years in boys and 9.7 years in girls.

Table 3 Results of 3 years of GH therapy in patients included in 3 French protocols

	Baseline			3 years				
	CA (years)	Height (SDS)	BA (years)	CA (years)	Height (SDS)	BA (years)	Δ height (SDS)	Δ BA (years)
<i>Trial 1</i>								
Control	4.3 ± 1.4	-2.8 ± 0.5	3.9 ± 1.3	7.3 ± 1.4	-2.1 ± 0.3	7.8 ± 0.7	$+0.7 \pm 0.5$	3.9 ± 0.7
0.7 U/kg/w	5.3 ± 1.4	-3.3 ± 0.6	4.0 ± 1.3	8.3 ± 1.4	-1.9 ± 0.9	8.0 ± 1.0	$+1.2 \pm 0.4$	4.0 ± 1.2
1.4 U/kg/w	5.7 ± 1.7	-2.9 ± 0.8	4.8 ± 1.4	8.7 ± 1.7	-1.6 ± 0.8	9.0 ± 1.1	$+1.5 \pm 0.4$	4.2 ± 1.0
<i>Trial 2</i>								
0.4 U/kg/w	8.4 ± 0.6	-3.1 ± 0.1	6.9 ± 0.7	11.4 ± 0.6	-2.4 ± 0.3	10.3 ± 1.2	$+0.7 \pm 0.3$	3.4 ± 0.8
1.2 U/kg/w	8.1 ± 0.3	-3.2 ± 0.2	6.0 ± 1.3	11.1 ± 0.3	-1.6 ± 0.1	9.8 ± 0.7	$+1.6 \pm 0.1$	3.8 ± 0.6
<i>Trial 3</i>								
1.4 U/kg/w	4.8 ± 1.8	-3.3 ± 0.6	3.5 ± 1.7	7.8 ± 1.8	-1.3 ± 0.9	7.3 ± 2.0	$+2.0 \pm 0.8$	3.8 ± 1.9

Fig. 1 Dose effect relationship.

Discussion

In the 3 French trials reported in this review, 3 years of GH therapy induced a catch up growth in prepubertal short children born with IUGR. The amplitude of the height gain at the

end of the third year is clearly related to the dose of GH administrated. With a relatively low dose of 0.4 U/kg/week the gain of + 0.7 SDS is absolutely identical to the spontaneous gain observed in the control group of trial 1. In this range of doses the use of GH appears as highly questionable. In contrast, when GH is given at

Table 4 Evolution of height during the year following GH cessation

	Height at 3 years (SDS)	Height at 4 years (SDS)	Δ height (SDS)
<i>Trial 1</i>			
0.7 U/kg/w	-1.4 ± 0.8	-1.9 ± 0.8	-0.5 ± 0.6
1.4 U/kg/w	-0.9 ± 0.7	-1.0 ± 0.4	-0.1 ± 0.2
<i>Trial 2</i>			
0.4 U/kg/w	-2.2 ± 0.3	-2.5 ± 0.4	-0.3 ± 0.2
1.2 U/kg/w	-1.6 ± 0.1	-1.8 ± 0.2	-0.2 ± 0.1

Table 5 Evolution of height in patients treated for 4 years (N=42)

	Height after 3 years (SDS)	Height at 4 years (SDS)	Δ height (SDS)
<i>Trial 1</i>			
0.7 U/kg/w	-2.0 ± 1.2	-1.8 ± 0.5	$+0.2 \pm 0.6$
1.4 U/kg/w	-1.8 ± 0.5	-1.5 ± 0.6	$+0.3 \pm 0.4$

doses ranging between 1.2 and 1.4 U/kg/week, the gain obtained in the 3 different trials analyzed here, varied between + 1.5 and + 2.0 SDS. As the initial mean growth deficit of the subjects enrolled in these trials was around - 3 SDS, the 3 years protocols were sufficient to normalize the height of the patients, or at least to move them to the lower half of the normal distribution of height. Moreover, the interpretation of these results must take into account the fact that mean parental heights were low in the 3 trials indicating reduced target heights in these children. Therefore it seems reasonable to conclude that the 3 years of GH therapy have induced a major benefit in this range of doses. The use of doses higher than those used in these 3 studies has also been proposed (9).

An increased rate of epiphysial maturation was observed in all the treated patients, without any reference with the dose. This acceleration of bone age, 3.84 years in mean during the 3 years of therapy, leads to a reduction of the expected benefit in terms of final height prognosis.

The improvement of adult height when low doses of GH are used is certainly questionable, as observed in the patients reported by Stanhope *et al.* (10). However the increased rate of bone maturation was also observed in the control group of trial 1, and the role of GH therapy in this process is not evident. Nevertheless, the amplitude of the catch up growth induced by doses superior to 1 U/kg/week is sufficient to lead to a very significant improvement of final height prognosis, despite of the acceleration of bone maturation.

The interruption of GH is followed by a deceleration of growth velocity, with a loss of part of the benefit. This loss appears as extremely small, ranging between 0.1 and 0.5 SDS. In the 2 groups treated with doses over 1 U/kg/week the loss was respectively 0.1 and 0.2 SDS. The continuation of GH therapy for a fourth year leads to a stabilisation of the benefit with a limited increase in height of 0.2 to 0.3 SDS according to the dose. This limited effect does not justify a prolongation of therapy after 3 years, in respect

to the economic cost of such a prolongation and to the potential risk of prolonged administration of GH in non deficient children, even if no side effects were observed in our studies.

In these conditions it seems reasonable to expect that 3 years of GH therapy will improve the final height of these patients. However an influence of GH therapy on the timing and amplitude of the pubertal growth spurt cannot be excluded at the present time. In comparison with historical series (4), patients of trial 2 entered into puberty one year earlier in terms of chronological age, but with exactly the same level of bone maturation.

As the height at the onset of puberty is strongly correlated with the adult height in patients with short stature secondary to IUGR (4) this fact leads also allows us to predict a probable improvement of final heights in our patients.

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