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ORIGINAL ARTICLE

Anita Hokken-Koelega · Paul Mulder · Ria De Jong
Mark Lilien · Raymond Donckerwolcke
Jaap Groothof

Long-term effects of growth hormone treatment on growth and puberty in patients with chronic renal insufficiency

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Abstract Several prospective trials have shown that recombinant human growth hormone (GH) accelerates growth significantly during the first years of therapy, but the effects of long-term GH therapy with regard to long-term growth response and safety have not yet been established. Forty-five Dutch prepubertal children [28 boys, 17 girls, mean (SD) age 7.8 (3.4) years] with chronic renal insufficiency (CRI) and severe growth retardation started GH therapy between 1988 and 1991 within one of the randomized Dutch trials. Long-term GH therapy, in this study a maximum of 8 years, resulted in a sustained and significant improvement of height standard deviation score (SDS) compared with baseline values ($P<0.001$). The mean height SDS reached the lower end (-2 SDS) of the normal growth chart after 3 years of GH therapy. During the following years the mean height SDS gradually increased, thereby approaching the mean target height SDS after 6 years of GH therapy. Three factors were significantly associated with the height SDS after 4 years of GH therapy: height SDS at the start (+) of therapy, age at the start of therapy (-), and the duration of dialysis treatment (-). Bone maturation did not accelerate during long-term GH therapy. Children on a conservative regimen at the start of GH therapy had no accelerated deterioration of renal function during 6 years of GH therapy. The average daily GH dose administered over the years had no significant influence on the glomerular filtration rate after 4 years. GH therapy had no adverse effects or significant effect on parathyroid hormone concentration, nor were there any radiological signs of renal osteodystrophy. Puberty started at a median age, within the normal range, of 12.4 years in boys and 12.0 years in girls, respectively. Long-term GH therapy leads to a sustained improvement in height SDS in children with growth retardation secondary to CRI, resulting in a normalization of height in accordance with their target height SDS, without evidence of deleterious effects on renal function or bone maturation. A GH dosage of 4 IU/m^2 per day appears efficient and safe. Our long-term data show that final height will be within the normal target height range when GH therapy is continued for many years.

Key words Long-term growth hormone therapy · Growth · Puberty · Chronic renal insufficiency

A. Hokken-Koelega
Department of Pediatrics, Division of Endocrinology, Sophia Children's Hospital and Erasmus University, Rotterdam, The Netherlands

P. Mulder
Department of Epidemiology and Biostatistics, Erasmus University, Rotterdam, The Netherlands

R. De Jong
Department of Pediatrics, Division of Nephrology, Radboud University Hospital, Nijmegen, The Netherlands

M. Lilien · R. Donckerwolcke
Wilhelmina Children's Hospital/University Hospital, Utrecht, The Netherlands

J. Groothof
Academic Medical Center, Amsterdam, The Netherlands

A. Hokken-Koelega (✉)
Department of Pediatrics, Division of Endocrinology, Sophia Children's Hospital, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands
e-mail: Hokken@alkg.azr.nl
Fax: +31-10-4636811

Introduction

Growth retardation occurs in many children with chronic renal insufficiency (CRI). During the last 10 years several short-term studies have convincingly shown that recombinant human growth hormone (GH) therapy at a dose of 4 IU/m^2 per day accelerates growth significantly in children with CRI, without accelerating bone maturation [1–5]. However, the long-term effects of GH therapy with regard to growth, bone maturation, and safety have not been established. We therefore evaluated the long-term data of patients participating in the Dutch randomized GH trials of children with growth retardation secondary to CRI, assessing the long-term efficacy and safety of GH therapy.

Patients and methods

The study population comprised 45 prepubertal children with CRI (28 boys, 17 girls) at the start of GH therapy. Their median age was 7.3 years (interquartile range 5.2–10.0 years). The study was approved by the ethics committee of each participating center. Written informed consent was obtained from the parents.

Inclusion criteria were: (1) CRI for at least 1 year with a glomerular filtration rate (GFR) below 20 ml/min per 1.73 m^2; (2) growth retardation determined by a height standard deviation score (SDS) for chronological age ($hSDS_{CA}$) under –1.88 [6], with a height velocity (HV) for CA below the 50th percentile [7] or a $hSDS_{CA}$ below 0.0 with a HV for CA below the 25th percentile; (3) prepubertal (Tanner stage I) [7]; (4) bone age <10 years for girls and <12 years for boys [8]; (5) no evidence of a specific cause of growth retardation other than CRI; (6) normal serum thyroid hormone levels and normal blood acid-base values; (7) no clinical or radiographic signs of osteodystrophy; (8) no previous treatment with anabolic steroids or sex steroids. At the start of GH therapy, 18 patients were on peritoneal dialysis, 9 on hemodialysis (HD), and 18 were managed conservatively. All children were on a standard diet, with a protein intake based on safe levels for age recommended by the World Health Organization. The standard protocol included phosphate-binding medication, calcium supplements, and 1.25-dihydroxyvitamin D. All dialyzed patients and 14 patients on conservative therapy were treated with recombinant human erythropoietin for severe anemia secondary to CRI, and the dose was regulated to maintain the hemoglobin concentration at approximately 5–6 mmol/l.

The patients participated in one of the Dutch randomized GH trials, starting between 1988 and 1991. Sixteen patients received either 4 IU/m^2 per day recombinant human GH or placebo for 6 months, after which they crossed-over to the alternative treatment for a further 6 months, followed by 4 IU/m^2 per day GH therapy [2]. Twenty patients were randomly assigned to receive either 2 or 4 IU GH/m^2 per day for 2 years, followed by 4 IU/m^2 per day GH therapy [3]. Nine patients received 4 IU/m^2 per day from the start. GH therapy, 4 IU/m^2 per day being roughly equal to 0.05 mg/kg per day, was administered once daily by subcutaneous injection.

Patients were examined at the time of enrollment and subsequently every 3 months for many years at the various participating centers, but always by the same investigator (A.C.S.H.-K.). Height was measured with a Harpenden stadiometer, always at the same time of day, and this was repeated until three consecutive readings agreed within a range of 0.2 cm. Height was expressed as a height SDS for chronological age, based on the Dutch reference values for healthy children [6]. We also expressed height as a height SDS corrected for target height (TH) SDS (THSDS). TH was calculated according to the formula: [(height father + height mother + 12)/2)] + 3 for boys and {[(height father + height mother – 12)]/2} + 3 for girls, with 3 representing the secular trend in centimeters. The TH calculation was only possible when the height of both parents was known. THSDS was calculated using Dutch references of mean (SD) adult men and women [6]. Bone age was always determined by the same investigator at the start of the study and subsequently every 6 months, using the TW2-RUS method [8].

Blood and urine samples were taken at each examination for determination of complete blood cell count, serum electrolytes, urea nitrogen, creatinine, calcium, phosphate, alkaline phosphatase, and urine glucose, protein, blood, and sediment. Additional blood samples were taken at the start of the study and subsequently every 6 months for other laboratory analyses. After centrifugation, samples were frozen (-20° C) prior to assay. Concentrations of intact plasma parathyroid hormone were measured with a two-step immunochemical method [9]. GFR was calculated by the formula proposed by Morris et al. [10], based on serum creatinine levels.

Results are expressed as mean (SD) unless stated otherwise. Student's *t*-test was used to determine changes from baseline. The Wilcoxon signed rank test was used for changes within groups; the Mann-Witney U test and chi-squared test were used for differences between groups. Correlations were assessed with the non-parametric Spearman's rank correlation test. The influence of various independent variables on a dependent variable was assessed by multiple regression analysis.

Table 1 Baseline clinical data for 45 patients with chronic renal insufficiency (CRI) (*SDS* standard deviation score)

Number (*n*)	45
Male/female	28/17
Age (years)	7.3 (5.2–10.0)[a]
Bone age (years)	6.3 (4.1–8.7)[a]
Height SDS (SD)	–2.96 (1.0)
Target height SDS (SD)	–0.21 (0.7)
Renal treatment (*n*)	
Conservative	18
Peritoneal dialysis	18
Hemodialysis	9

[a] Median (interquartile range, 25th to 75th percentile)

Results

Table 1 shows the baseline clinical data for all 45 patients, 11 of whom completed 6 years and 7 of whom completed 8 years of GH therapy. All but 1 patient dropped-out due to kidney transplantation, none due to non-compliance or lack of interest. One patient died accidentally during surgical replacement of a peritoneal drain. The subcutaneous injections were well tolerated, even in the youngest patients and also after many years of GH therapy. No GH-related adverse effects were seen.

Growth

Table 2 shows the effect of long-term GH therapy on the mean (SD) height SDS, the height SDS corrected for THSDS, and bone maturation. There was a significant increment in mean (SD) height SDS over baseline values ($P<0.001$), both in the total group of children with intermediate- and long-term GH therapy ($n=45$) as well as in those treated with GH therapy for 6 ($n=11$) and 8 years ($n=7$), respectively. Figure 1 shows the significant improvement in mean height SDS during long-term GH therapy. The mean height SDS reached the lower end (–2 SDS) of the reference growth chart after 3 years of GH therapy. During the ensuing years, the mean height SDS gradually increased, approaching the mean THSDS after 6 years of GH therapy. After 6 years of GH therapy, the mean height SDS was no longer significantly different from the mean THSDS. Two boys who started GH therapy before the age of 11 years reached a final height of 179.7 and 171.6 cm, respectively. Two girls who started GH before the age of 10 years reached a final height of 153.5 and 175.5 cm, respectively, well within their TH range. The data on height SDS during the first years of GH therapy of those who received GH therapy for 8 years were not significantly better or different from those who randomly dropped-out during the years due to renal

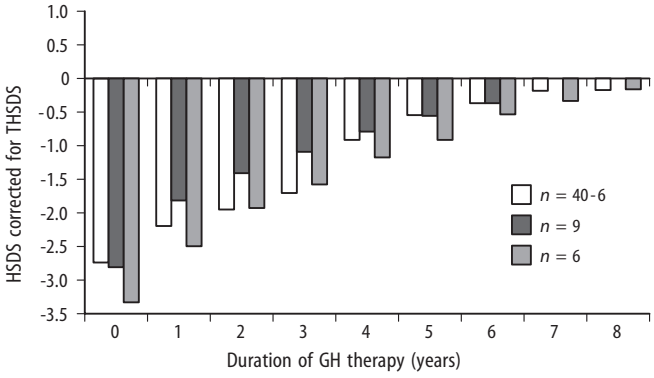

Fig. 1 Mean height standard deviation score (*HSDS*) corrected for target height SDS (*THSDS*) during 8 years of growth hormone (*GH*) therapy in patients with chronic renal insufficiency (CRI). Group *n*=40–6, data of 40 patients at start of GH therapy decreasing to 6 patients treated for 8 years; group *n*=9, data of 9 patients treated with GH for 6 years; group *n*= 6, data of 6 patients treated with GH for 8 years

Table 2 Effects of long-term growth hormone (GH) therapy on mean (SD) height SDS, height SDS corrected for target height and bone maturation (ΔBA/ΔCA) in CRI patients (*BA* bone age, *CA* chronological age)

	Total group		Group treated for 8 years	
	n	Mean (SD)	*n*	Mean (SD)
Height SDS				
At start	45	–3.0 (1.0)	7	–3.4 (0.9)
Year 2	26	–2.2 (1.5)*	7	–2.5 (0.8)*
Year 4	17	–1.3 (1.3)*	7	–1.7 (0.8)*
Year 6	11	–0.9 (1.1)*	7	–1.1 (1.0)*
Year 8	7	–0.8 (1.4)*	7	–0.8 (1.4)*
Height SDS corrected for target height SDS				
At start	40	–2.7 (1.0)	6	–3.3 (0.8)
Year 2	24	–2.0 (1.5)*	6	–1.9 (0.8)*
Year 4	15	–0.9 (1.2)*	6	–1.2 (0.7)*
Year 6	9	–0.4 (1.0)*	6	–0.5 (0.9)*
Year 8	6	–0.2 (1.3)*	6	–0.2 (1.3)*
ΔBA/ΔCA				
0–2 years	20	1.05 (0.5)**	6	1.00 (0.2)**
0–4 years	15	1.05 (0.2)**	6	1.06 (0.4)**
0–6 years	6	1.10 (0.4)**	6	1.10 (0.4)**

* $P<0.001$ compared with start; **not significantly different from 1.00

transplantation. Hence their growth data represent the effect of long-term GH therapy in children with growth retardation due to CRI.

One older prepubertal boy, aged 16.1 years at the start of GH therapy, had a very limited growth response. He had been on HD treatment for almost 10 years when he started GH. He did not enter puberty during GH therapy. Prestudy HV was 0.2 cm/year. During 3.5 years of GH therapy, with a dose of 4 IU/m^2 per day, his height increased from 135.4 cm at the start to 144.4 cm at the end of treatment. This patient was an exception.

Table 3 Multiple regression analysis on the change in height SDS during 4 years of GH therapy in children with CRI (*SE* standard error)

Variable	Regression coefficient	SE	*P* value
Height SDS at start	0.85	0.23	0.004
Age at start	–0.17	0.08	0.05
Percentage of time on dialysis	–1.03	0.49	0.05

In order to evaluate the influence of various variables on the change in height SDS during GH therapy, a multiple regression analysis was performed with the change in height SDS after 4 years of GH therapy as the dependent variable (Table 3). Independent variables were: the height SDS and the age at the start of GH therapy, the average daily GH dose administered during 4 years of GH therapy (expressed as mean IU GH /m^2 per day), and the percentage of time on dialysis during GH therapy. A higher height SDS at the start of GH therapy was associated with a significantly higher height SDS after 4 years of GH therapy (P=0.004), indicating that the height SDS after 4 years will be 0.85 higher in a child whose height SDS at the start is 1 SDS higher than that of another child, provided other factors are equal. A younger age was significantly associated with a higher height SDS after 4 years (P=0.05), each year being associated with a better height SDS of 0.17, provided the other factors are equal. A longer duration of dialysis treatment was associated with a lower height SDS after 4 years than conservative treatment (P=0.05). Dialysis treatment during 4 years of GH therapy resulted in a height SDS of 1.0 SDS lower than in patients on conservative treatment during 4 years of GH therapy, provided other factors were equal. The average daily GH dose administered during 4 years had no significant influence on the height SDS after 4 years (P=0.58).

Bone maturation, expressed as delta bone age divided by delta chronological age, was not significantly different from 1, i.e., it did not accelerate during long-term GH therapy (Table 2).

Glomerular filtration rate

Eighteen children were managed conservatively at the start of the study. Their mean (SD) GFR was 16.3 (6.2) ml/min per 1.73 m^2. Eleven children entered dialysis or received a successful renal allograft without prior dialysis. Two children, having a stable GFR while managed conservatively, received a rapidly deteriorating renal allograft from a living-related donor. They started dialysis within 1 week of renal transplantation, returned to GH therapy within a few weeks, and continued GH until the 8-year time point. After 4, 6, and 8 years of GH therapy, respectively, 11, 8, and 5 children were still managed conservatively. The mean (SD) GFR of the 8 children who received GH therapy for 6 years was 17.2 (5.2)

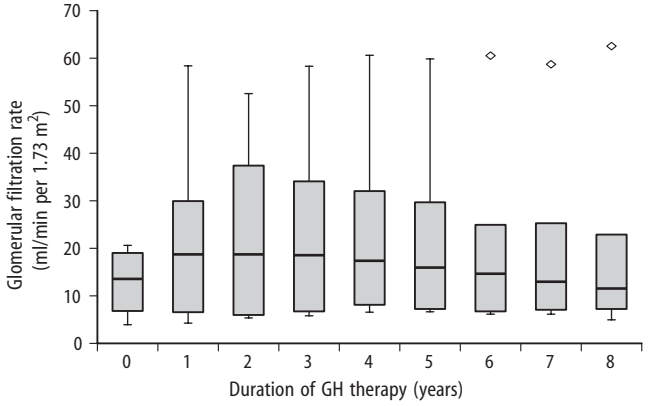

Fig. 2 Median glomerular filtration rate during 8 years of GH therapy in the total group of CRI patients. Number of patients (*n*) after 0, 2, 4, 6, and 8 years: 45, 26, 17, 11, and 7, respectively

at baseline and 19.7 (10.5) ml/min per 1.73 m^2 after 6 years of therapy with an average GH dose of 3.8 IU/m^2 per day. Figure 2 shows the median GFR levels in the total group, at the start and after 2, 4, 6, and 8 years in 45, 26, 17, 11, and 7 patients, respectively.

In order to evaluate the influence of various variables on the change in GFR in patients managed conservatively during GH therapy, we performed a multiple regression analysis with the GFR after 4 years of GH therapy as the dependent variable. Independent variables were the average daily GH dose administered during the years (expressed as mean IU GH /m^2 per day) and the GFR at baseline. Both variables had no significant influence on the GFR after 4 years (*P*=0.80 and 0.68, respectively).

Pubertal development

At the start of GH therapy all children were prepubertal, but 6 children were already 11 years or older. The start of puberty was evaluated in 24 boys aged less than 11 years and in 14 girls aged less than 10 years at the start of GH therapy. Fourteen boys dropped-out before the age of 11 years, all but one due to renal transplantation. The remaining 10 boys entered puberty during GH therapy at a median age of 12.4 years (interquartile range 11.5–13.4 years), i.e., within the normal range for healthy boys. At the start of puberty the mean height SDS was – 0.5. None of the boys started puberty later than the age of 13.6 years.

Of the 14 girls, 9 dropped-out due to renal transplant before the age of 10 years. The remaining 5 girls entered puberty during GH therapy at a median age of 12.0 years (interquartile range 10.8–13.0 years), i.e., within the normal range for healthy girls.

At the start of puberty the mean height SDS was –1.9. None of the girls started puberty later than 13.4 years. Data on the age at menarche are not yet available, since most girls are still too young for menarche. Interestingly, puberty also started at a normal age in all GH-treated boys and girls on long-term dialysis treatment, a group previously considered at risk for delayed pubertal development.

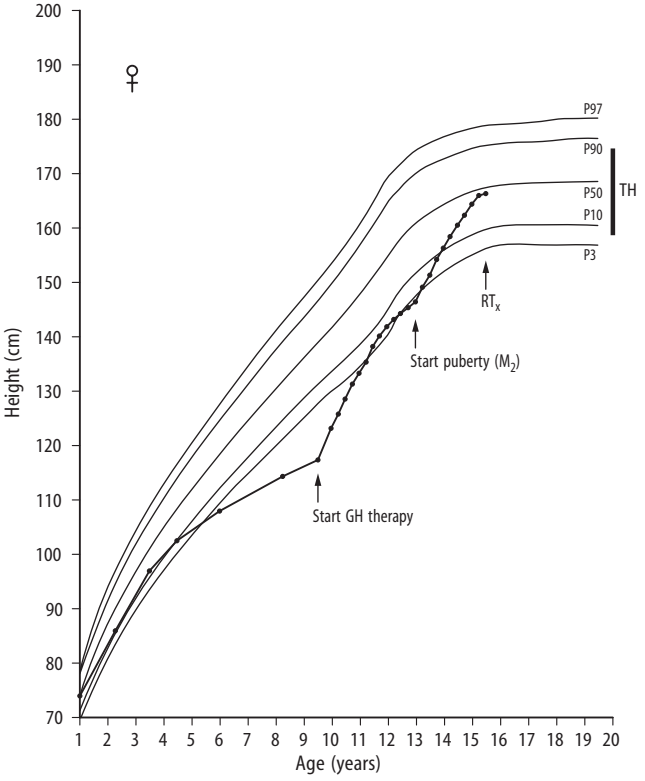

Fig. 3 Individual growth chart of a girl treated with GH therapy for many years, showing a prepubertal dip in height velocity during the period prior to the start of puberty (*RTx* renal transplant, *TH* target height)

Other variables

Throughout the study, there were slight but not significant time-related changes in serum sodium, potassium, calcium, phosphate, urea nitrogen, parathyroid hormone, free thyroid hormone, and thyroid-stimulating hormone in all patients. Alkaline phosphatase increased significantly during the 1st year of GH therapy and remained stable thereafter.

Discussion

The presented data clearly show that long-term therapy with recombinant human GH at an average dose of 3.8 IU/m^2 per day results in a sustained and significant improvement in height in children with growth retardation due to CRI, resulting in a normalization of height in accordance with their THSDS. During the first years of GH therapy, a marked catch-up growth is seen. A more-gradual but still significant increase in height SDS is observed during the following years due to the fact that the height of the children is nearing their genetic growth percentile, i.e., the THSDS.

During long-term follow-up, it became apparent that the growth chart of the children on long-term GH therapy demonstrated a normal growth pattern, including signs of the so-called prepubertal dip. This phenomenon is seen on the growth charts of healthy boys and girls when frequent longitudinal measurements have been recorded. During the prepubertal dip HV drops for 6–9 months prior to the start of puberty. It has been suggested that the GH receptors are less sensitive to GH during the period just prior to the start of puberty, probably due to hormonal changes. Interestingly, this phenomenon also occurs in the children with CRI on GH therapy. The fall in HV, however, may cause concern about the efficacy of the GH therapy when one does not realize that it might be due to a prepubertal dip. Figure 3 depicts an individual growth chart of a girl demonstrating the prepubertal dip. The same underlying mechanism of the prepubertal dip may also play a role in the disappointing growth during GH therapy in older prepubertal boys with severely delayed puberty.

The height SDS at the start was positively associated with the gain in height SDS during 4 years of GH therapy, suggesting that GH therapy should best be started before a serious reduction in height SDS has occurred. This finding contrasts with that in children with growth retardation secondary to other causes, such as growth hormone deficiency. Under these conditions a lower height SDS is associated with a better gain in height SDS during GH therapy, even after correction for regression to the mean. We have earlier reported that growth in children with CRI both before and during GH therapy was negatively associated with serum levels of insulin-like growth factor binding proteins (IGFBPs). This suggests that the more severe the growth retardation the higher the levels of serum IGFBPs and the lower the bioavailability of insulin-like growth factors [3]. This might explain the differences in growth between children with CRI and those with growth deficiency due to other problems, and why one should start GH therapy before the height SDS has seriously dropped, i.e., before the growth-inhibiting IGFBPs have increased too much, in children with CRI. Younger age at the start of treatment results in a better height SDS, whereas dialysis treatment has a negative effect on the gain in height SDS during 4 years of GH therapy. The average daily GH dose administered during 4 years had no significant influence on the gain in height SDS after 4 years of treatment, probably because the average daily GH dose had only very limited variation, as most children were treated in the long-term with a dose of 4 IU GH/m^2 per day.

Our report is one of the first of the long-term effects of 8 years of GH therapy in a selected group of children with growth retardation due to CRI and a relatively low GFR (<20 ml/min per 1.73 m^2) at the start of GH treatment. The growth results during the first 2–4 years are comparable with those of other studies evaluating the effects of GH therapy in children with growth retardation secondary to CRI [1–5].

Long-term GH therapy did not result in acceleration of bone maturation. These data indicate that long-term GH therapy does not merely result in sustained improvement of growth over the years, but also in attainment of a final height in accordance with the genetic growth potential.

Our study shows that long-term GH therapy does not result in accelerated deterioration of renal function in children who are managed conservatively. Two children with a baseline GFR between 15 and 20 ml/min per 1.73 m^2 had a considerable improvement in renal function during GH therapy, which was sustained for 8 years, while 3 children with a baseline GFR of 10–15 ml/min per 1.73 m^2 did not start dialysis during 8 years of GH therapy. The average GH dose administered over the years (expressed as mean IU GH /m^2 per day) and the GFR at baseline had no significant influence on the GFR after 4 years of GH therapy in the 18 patients managed conservatively at baseline.

GH therapy had no adverse effects and did not induce significant changes in the parathyroid hormone concentrations, nor were there any radiological signs of renal osteodystrophy during the study. The serum alkaline phosphatase concentration increased during the 1st year of GH therapy, but remained stable thereafter. The increase in serum alkaline phosphatase seems to reflect osteoblastic activity due to the catch-up growth resulting from GH therapy.

Our data demonstrate that long-term GH therapy leads to a sustained and significant improvement of height in children with growth retardation secondary to CRI, resulting in a normalization of height in accordance with their THSDS, without evidence of deleterious effects on renal function or bone maturation. GH therapy should best be started before the growth retardation becomes considerable, a GH dose of 4 IU/m^2 per day appears efficient and safe for long-term growth. Optimization of height prior to the first renal transplantation is very important for future growth and final height. Although growth retardation in children with CRI is an indication for GH therapy in many countries, GH should not be used indiscriminately in all children with CRI. It remains important to register and follow the patients via large registration databases. Further studies should be directed at optimizing individual GH modalities and generating long-term safety data.

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