American Journal of BioMedicine
AJBM 2020;8(2):112-118
Research Article doi:10.18081/2333-5106/017-3/125-131

Response of children with short stature to recombinant human growth hormone (rhGH) after the first year of therapy

Rajaa Jabbar kadhum [1*]

Abstract

Short stature is the most common cause of referral to a pediatric endocrine unit. The primary goal of rhGH therapy is attaining normal adult height. The objective of this study is to determine the response of children with short stature to rhGH after one year of therapy. The study was done on 110 children with short stature, their age range was 3-14 years they received regular rhGH in a dose of 0.24-0.3 mg/kg/week and their response was followed during the first year of therapy by bone age, anthropometric measurements and height velocity. Growth hormone deficiency was the leading cause of short stature contributing to 84.5%. There was a significant increase in mean height velocity after one year of rhGH therapy (7.1±3.5cm per year) which is almost the double pretreatment height velocity. The catch-up growth was slow in the first 6 months of therapy & and there was a significant increase in bone age at the end of the first year. The lowest response in mean height velocity was in prepubertal children 3-5 years of age (1.54±0.44 cm per year). We conclude that the growth was slow during the first six months but there was significant growth at the end of the first year of therapy with a doubling of the height velocity and a significant increase in bone age. The response was slow in the prepubertal age.

Keywords: Response; Short stature; rhGH; Height measurements; Height velocity

*Corresponding Author: Rajaa Jabbar Kadhum
[1]Department of Pediatric, Faculty of medicine, Kufa University
Received January 27, 2020; Accepted May 01, 2020; Published May 27, 2020

Introduction

Treatment with rhGH is indicated for children with short stature or growth failure associated with a number of conditions in which there is a deficiency of, or a decreased responsiveness to endogenous growth hormone. The use of growth hormone is approved by the US Food and Drug Administration for the treatment of growth failure associated with growth hormone deficiency and short stature associated with Turner syndrome, Noonan syndrome, children borne small for gestational age, chronic kidney disease, Prader Willi syndrome and idiopathic short stature [1]. Growth response is heterogenous and influenced by the interplay of auxological, environmental, and genetic factors. There is high individual variability and a significant number of patients do not attain an adult height within the familial target range showing unsatisfactory response this observation should lead to a more optimal growth hormone therapy [2]. The adult height of patients treated with growth hormone is influenced by the height gained during the course of therapy, the rate of bone maturation, and the onset of puberty [3]. Growth hormone dose and growth hormone response during the first year of therapy are strong predictors of final height outcome in prepubertal growth hormone treated children with growth hormone deficiency, a first year increase of 0.5 SDS corresponds to an average height gain of approximately 1.0 SDS [4, 5].

doi:10.18081/2333-5106/017-3/125-131

Research Article

Method

A prospective study was done on 110 children with short stature [boys 71 constituting 64.55%, and girls 39 constituting 35.45%]. Their age range was 3-14 years (mean age 9.6 ± 2.7) who were referred to the endocrine clinic in Al Zahraa hospital in Najaf city in Iraq. The period of the study is from 1rst of Jan. 2012 to 31rst of Dec. 2014. Written parental permission consent was used for inclusion of their children in this study. Information collected from each patient included:

1- Detailed medical history concentrating on date of birth, mode of delivery, onset of slow growth, any associated medical illness or medications used and family history of slow growth or short stature.
The dose remained unchanged in the first year of treatment.
Follow up: the patients were followed for one year. All anthropometric procedures were performed at baseline before treatment &followed every 3 months in addition to compliance to therapy and side effect of the drug by the same observer and at the same time of the day (8 am-1pm)in endocrine clinic .skeletal maturity was followed after 6 months and 12 months of therapy. Statistical analysis was done by using SPSS (statistical package for social science) version 20 in which we use paired *t*- test to compare at different times and persion correlation coefficient to find association between two continuous variables; we set P value < 0.05 as significant.

2- Complete physical examination including anthropometric measurements as: - Body weight (Kg) was assessed in light clothing without shoes using a calibrated electronic scale (TANITA HD 309). - Height measurement (cm) by studiometer of seca (France mode, sensitive to 10 mm). done by the researcher. The height and weight were assessed according to Tanner and Whitehouse growth charts. a height >2 SD below the mean for age & sex was considered as short stature - The lower segment of the body was measured from the symphysis pubes to the floor & the US: LS ratio was calculated. - Occipito-frontal circumference (cm) was measured by using tape measure. 3- Skeletal maturation was determined by bone age obtained from an AP radiograph of the left hand & wrist joint using Greulich and Pyle atlas. 4- Laboratory investigations done to the patients include complete blood count, general urine examination, general stool examination, thyroid function test, growth hormone assay (basal and provocation test by clonidine 75-100mcg/m2). Other test as karyotype for girls to exclude Turner syndrome and jejunal biopsy in those suspected to have celiac disease. Therapy: all patients were treated with rhGH (Novo –Nordisk, Denmark) in a dose of 0.24-0.3 mg/kg/week divided over 6 days and given subcutaneously.

The dose remained unchanged in the first year of treatment. Follow up: the patients were followed for one year. All anthropometric procedures were performed at baseline before treatment & and followed every 3 months in addition to compliance to therapy and side effects

doi:10.18081/2333-5106/017-3/125-131

Research Article

of the drug by the same observer and at the same time of the day (8 am-1 pm)in the endocrine clinic .skeletal maturity was followed after 6 months and 12 months of therapy. Statistical analysis was done by using SPSS (statistical package for social science) version 20 in which we use paired t-tests to compare at different times and a person correlation coefficient to find an association between two continuous variables; we set P value < 0.05 as a significant.

Results

The study was done on 110 children with short stature, their chronological age range was 3-14 years, and the mean of bone age was 5.0854 years. Seventy-one (64.55%) were boys & 39(35.45%) were girls. The commonest cause of short stature was growth hormone deficiency (84.5%) as shown in table (1). There was a statistically significant increase in weight, height measurements & and bone age after 12 months of rhGH therapy in comparison to pretreatment values (P- value <0.01) as shown in Table (2). The increase in height during the first 6 months of therapy was not statistically significant (pair 2 table 2). The height velocity mean standard deviation at prepubertal children in this study was less than that at pubertal age & and lowest at age of 3-5 years (1.54±0.44 cm per year) as shown in Table (3). Children in our study showed a significant increase in mean height velocity after one year of rhGH therapy (7.1±3.5cm per year).

Table 1.

Frequency of causes of short stature among studied sample.

Cause of short stature	Frequency	Percent
GH deficiency	93	84.5
Constitutional	3	2.7
Malnutrition	3	2.7
Celiac disease	3	2.7
Turner syndrome	3	2.7
Diabetes mellitus	2	1.8
Silver Russell	2	1.8
Panhypopituitarism	1	0.9
Total	110	100

doi:10.18081/2333-5106/017-3/125-131

Research Article

Table 2.
Response of short stature children to rhGH after 6months & 12 months follow up in regard to body weight, height measurements & bone age.

Growth parameter		Mean	Std. Deviation	P value
Pair 1	weight at admission	18.0915	6.86920	0.131
	Weight after 6 months	20.5366	15.57435	
Pair 2	height at admission	108.5000	16.20776	0.252
	height after 6 months	120.0793	90.29579	
Pair 3	Bone age at admission	5.0854	2.75955	<0.001
	Bone age after 12 months	7.1037	2.77526	
Pair 4	Weight after 6 months	20.5366	15.57435	0.634
	weight after 12 months	21.3110	7.31084	
Pair 5	height after 6 months	120.0793	90.29579	0.658
	height after 12 months	115.5915	15.01196	
Pair 6	weight at admission	18.0915	6.86920	<0.001
	weight after 12 months	21.3110	7.31084	
Pair 7	height at admission	108.5000	16.20776	<0.001
	height after 12 months	115.5915	15.01196	

Table 3.
Response of children with short stature according to chronological age

Age (years)	No. of patients	Mean ±SD	Range
3-5	21	1.54±0.44	1-2.5
6-8	26	3.4±1.6	2-5.5
9-11	39	2.36±1.13	1-5
12-14	24	2.5±1.3	1-5

Table 4.
Mean height velocity of short stature children before and after 12 months of rhGH treatment.

Short stature children (n=110)	Height velocity mean+_SD	Range
Pretreatment	3.2±1.25cm/y	1.5 - 4.3
12 months after treatment	7.1±3.5cm/y	2 - 11

P=0.002

doi:10.18081/2333-5106/017-3/125-131

Research Article

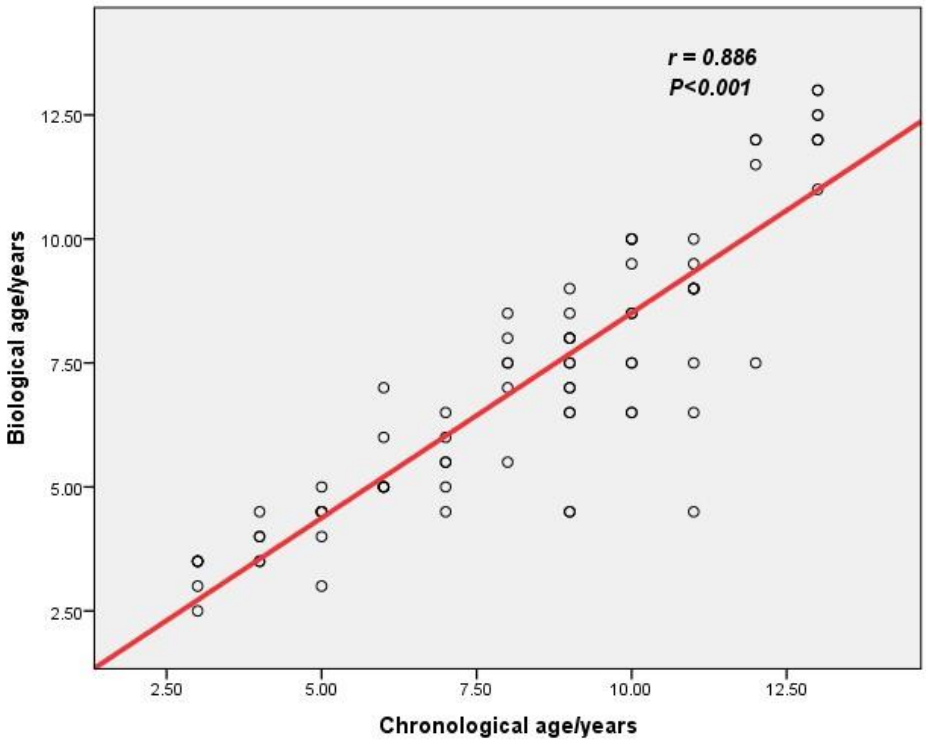

Figure 1.
Correlation between chronological age and biological age

Discussion

The most common cause of short stature beyond the first year or two of life are genetic short stature & constitutional growth delay which are normal non –pathologic variants of growth. Growth hormone deficiency accounts for 84.5% of causes of short stature among children attending the endocrine clinic in Najaf city in Iraq. Growth hormone deficiency was the cause of 69% of short children attending the endocrine clinic in Pakistan and 86% of patients in Saudi Arabia [6, 7]. Other studies in India showed that the commonest pathological cause of short stature was hypothyroidism and genetic disorders, followed by nutritional and musculoskeletal causes [8]. The reason for the predominance of pathological causes could be due to that this endocrine center is specialist referral center and most of the non pathological causes were excluded before referral and we need wider population based study for more accurate results about the commonest cause. The increase in height during the first 6 months of therapy was not statistically significant (pair 2 table 2) but the overall increase in height at the end of the first year of therapy was significant (pair 7 table 2). This finding was in disagreement with other

doi:10.18081/2333-5106/017-3/125-131

Research Article

studies which showed that the first 3 months of therapy was the fastest and predicts the final response to growth hormone therapy [9]. There is controversial debate on the value of short term measurements of height this parameter had been more or less ignored in the past [10]. The height velocity mean standard deviation at prepubertal children in this study was less than that at pubertal age and lowest at age of 3-5 years (1054±0.44 cm per year) as shown in table 3. This finding was in contrast with other study which conclude that the pubertal status at the onset of therapy as well as the sex, did not influence the height velocity in the first two years of therapy, however the increase in patient's height was proved to be significantly better among children in prepubertal period, rhGH treatment proved to be more effective for patients with total growth hormone deficiency with no signs of sexual maturity [11]. Treatment with rhGH should be started early to improve height as much as possible before the onset of puberty and the rhGH did not affect pubertal growth in children with idiopathic growth hormone deficiency [12]. Prepubertal children who show an appropriate first -year response to rhGH are likely to benefit from long –term treatment even on low dosage [5]. Other study found that starting high dose of rhGH to prepubertal children results in acceleration of bone maturation and early onset of puberty though it increases significantly height slandered deviations [13]. Children in this study showed significant increase in bone age at the end of one year of therapy. Retardation of bone age at the start of treatment indicates the long term history of disturbance of growth and if ossification is markedly delayed, a more pronounced catch up growth is to be expected. Bone age delay is to be considered as a predictive factor which may negatively influence the effect of rhGH therapy on final height in Turner syndrome patients [14]. The children in our study showed significant increase in mean height velocity after one year of rhGH therapy (7.1±3.5cm per year) which is almost the double of pretreatment height velocity. This good response could be attributed to the main cause of short stature in our study sample which was growth hormone deficiency. Doubling of the pretreatment height velocity at the end of the first year of therapy is considered as a predictor of successful rhGH [15] and the effectiveness of rhGH therapy can be evaluated by estimating the standardized height gain and the height velocity after the first year of therapy [16].

Conclusion

The growth was slow during the first six months of therapy but there was significant growth at the end of the first year of therapy with rhGH with doubling of the height velocity & significant increase in bone age. The response was slow in the prepubertal age.

References

1. Richmond E, Rogol AD. Current indications for growth hormone therapy for children and adolescents. *Endocr Dev* 2010;**18**:92-108.
2. Ranke MB, Lindberg A. Predicting growth in response to GH hormone treatment. *Growth hor. IGF research* 2009;**19**:1-11.

doi:10.18081/2333-5106/017-3/125-131

Research Article

3. Cohen P, Bright GM, Rogol AD. Effect of dose & gender on the growth and growth factor response to growth hormone in growth hormone deficient children implications for efficacy & safety. *J Clin Endocrinol Metab* 2002;**87**:90-8.
4. Reiter EO, Price DA, Witton P, Albertsson W. Effect of GH treatment on the near final height of 1258 patients with idiopathic GHD: analysis of a large international data base. *J clin Endocrinol Metab* 2006;**91**:2647-45.
5. Ranke MB, Lindberg A, Price DA, *et al*. Reiter EO: KIGS International board. Age at growth hormone therapy start & first year responsiveness to GH are major determinants of height outcome in idiopathic short stature. *Hom Res* 2007;**68**(2):53-6.
6. Jawa A, Riaz SH, Khan A, sir MZ, Afreen B. Causes of short stature in Pakistani children found at an endocrine center. *Pak. J Med sci* 2016;**32**(6):13211325.
7. AL-Ruhaily AD, Malabu UH. Short stature in Saudi Arabia :etiologic profile in adult endocrine clinic. *Niger J Med* 2009;**18**(3):268-71.
8. Ganavi R, Jaishree V. Clinical and etiological profile of children with pathological short stature. *int J Contemp pediatr* 2017;**4**(1):73-77.
9. Eckhard S, Frank W, Frank R, *et al*. A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. *European J. of endocrinology* 2001;**144**:13-20.
10. Voss LD. Can we measure growth? *Journals of medical screening* 1995;**2**:164-167.
11. Agnieszka Z, Wioletta L, Urszula T, Agieszka M. The influence of selected factors on the effectiveness of rhGH replacement therapy in children with growth hormone deficiency. *Endokrynol, ped* 2014;**4**(49):19-26.
12. Rekers-Mombarg LT, Kamp GA, Massa GG, Wit JM. Influence of growth hormone treatment on pubertal timing and pubertal growth in children with idiopathic short stature. Dutch Growth Hormone Working Group. *J Pediatr. Endocrinol Metab* 1999;**12**(5):611-22.
13. Kamp GA, Waelkens JJ, de Muinck Keizer-Schrama SM, *et al*. High dose growth hormone treatment induces acceleration of skeletal maturation and an earlier onset of pubertal children with idiopathic short stature. *Ach Dis Child* 2002;**87**(3):215-220.
14. Nagwa AM, Nermeen SE M, Fatma A, Tarek MF. Bone age is the best predictor of growth response to recombinant human growth hormone in Turner syndrome. *Indian journal of human genetics* 2010;**16**(3):119-26.
15. Schonau E, Westermann F, Rauch F, *et al.* A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. *Eur J Endocrinol* 2001;**144**(1):13-20.
16. Ireno L, Allessandro M, Silvia V, *et al*. Predictors of response to rhGH treatment in 125 children with short stature with various etiologies. *European society of pediatrics endocrinology abstracts* 2015;**84**:3-951.