Response to Recombinant Human Growth Hormone Therapy in Libyan Children with Growth Hormone Deficiency in Misurata

By
Najla Alssdig Maiteeg, Sabrin Adel Elssadawi, Fatima Ali Gheddafi
Faculty of Pharmacy, Department of Biomedical Sciences, Misurata University

ABSTRACT

Recombinant growth hormone (rhGH) is used for the treatment of growth hormone deficiency (GHD). Children with growth hormone deficiency characterized by short stature. The aim of this study was to assess the efficacy of rhGH as a therapeutic intervention for treatment of children with GHD in Misurata following a year of therapy. Medical records of 174 GHD children attended the department of pediatric endocrinology in the Misrata Specialized Center for Diabetes and Endocrine. From June 2012 to January 2022 were retrospectively evaluated. Among them 50 patients met the inclusion criteria of receiving the rhGH treatment for a year. The relevant anthropometric data at baseline and follow-up were recorded. A retrospective study that included 50 GHD children treated with rhGH was performed. Patients were divided into two groups according to treatment response: poor responders with average mean increase of height by < 3 cm/year and good responders with increase of height by ≥ 3 cm/year. Patients with idiopathic GHD constitute almost two-thirds of the pathogenesis of GHD (70 %). Forty-six patients (92%) showed good response (Δ height >3 cm after one year of therapy). The response to treatment were; 93% in the age group 3-5 years old, and 83% in the age group 10-12 years. The mean difference in the growth rate was ΔHV = 5.163 cm/year after one year of rhGH therapy. Our study demonstrated that the use of rhGH for one year has an promising effect on increasing the height of patients diagnosed with GHD. We highly recommend the early use of rhGH in with GHD.

Keywords: Growth hormone, Growth hormone deficiency, Recombinant growth hormone.

INTRODUCTION

Human GH is a 191 amino acid single-chain polypeptide which is synthesized and secreted by the somatotroph cells of the anterior lobe of the pituitary gland (1). As its name implies the GH has a crucial role in growth regulation during the childhood (2). The synthesis and release of GH are under the control of various hormones, including GH releasing hormone (GHRH). Concentrations of GH are higher in the fetal, neonatal and pubertal periods than in adulthood, and increase with chronic malnutrition, exercise, physical trauma and sepsis (3).

For corespondance:Najla alssdig Maiteeg,
Email: Manajla73@gmail.com

In children and adolescents, GH has a role in increasing bone length and density; however, GH is also important throughout life in increasing muscle mass, regulating lipid, carbohydrate metabolism and body water levels (4). Normal pulsatile GH secretion is crucial for postnatal growth and development, but not for intrauterine growth (5). As GH is secreted in a pulsatile manner (usually six pulses during 24 h, mainly during the night with low levels between pulses), random measurements of serum GH are of little value for the diagnosis of GHD (6,7). GH exerts its biological effects by binding to the extracellular domain of the GH receptor, a

single pass protein that also contains transmembrane and intracellular regions (8), this GH induced GH receptor dimerization is thought to be the first step in the signal pathway that ultimately results in the various biological effects associated with GH (9). GH is acting both directly and via its stimulation of insulin-like growth factor I (IGF I) production to promote linear growth (2). Growth hormone deficiency (GHD) results when the pituitary gland does not produce enough growth hormone to stimulate the body to grow and manifest as a slow or flat rate of growth in both early and later childhood (2). Children with GHD usually have typical body proportions, but are often chubbier, shorter, and may be perceived to be younger than their age when compared with peers of the same age and gender (10,11). The prevalence of childhood GHD is within the range of one in 3000 to one in 4000 (12,13). Although this is an probably overestimated in view of the reversibility of the deficiency in 25-75% of patients (14). However; according to different studies, the incidence of the deficiency is thought to vary substantially between countries, for example in the UK, estimates that GHD occurs in about one in every 3800 births (15). Another study in Belgium indicates an overall prevalence of GHD of 1 in 5600 (16). A recent study reported the incidence of childhood onset GHD to be 2.58 for males and 1.70 for females per 100,000 (17). Limited studies were performed in Libya to assess the efficacy of rhGH in improving height outcome in GHD pediatrics patients. Performing a study to investigate the use of rhGH for one year to treat GHD patients will contribute to the effectiveness of rhGH in treatment of GHD patients. The aim of this study was to assess the use of rhGH for one year in treatment of children with GHD in Misurata.

Patients and Methods

This is a cross-sectional retrospective study of GHD children treated with rhGH for one year in the Misrata Specialized Center for Diabetes and Endocrine. The Department of Pediatric Endocrinology at this center is the only department that treats GHD children. These children were under follow-up at the Department of Endocrine. The study was approved by the ethical committee .

Medical records of 174 GHD children (101 were males and 73 were females) attended the department of pediatric endocrinology in the Misrata Specialized Center for Diabetes and Endocrine. From June 2012 to January 2022 were retrospectively evaluated. Among them 50 patients met the inclusion criteria of receiving the rhGH treatment for a year. The relevant anthropometric data at baseline and follow-up were recorded. The height of these children at the study time > 2SD below the mean of comparable age and gender, aged (3-15) year. The medical records of identified patients were reviewed and data were extracted using data extraction form. The data included: a child age, age at the initiation of treatment, gender, average GH dose (mg/kg/day), cause of GHD, chronic disease data at baseline, height at start GH treatment, height after one year of rhGH treatment, final height expressed as standard deviation determined by the World Health Organization. First-year height velocity (HV) (cm/year), were calculated as the increment in height between start of treatment and a measurement made after 12 months of rhGH treatment. The observed first-year HV (cm/ year) was expressed as mean (SD). Data were also extracted on pubertal status of each patient which was documented according to the Tanner stage. Pre-pubertal status was defined as Tanner stag1. Response

to treatment was defined by acceleration of head growth in cm/year from the pre-treatment growth rate. Patients were divided into two groups according to treatment response: poor responders (ΔHV< 3 cm/year) and good responders (ΔHV ≥ 3 cm/year).

Statistical analysis:

IBM SPSS statistics 21® software was used for all statistical analyses. Descriptive statistics were performed to describe Baseline auxological characteristics of children.

RESULTS AND DISCUSSION

rhGH is used for the treatment of GHD. Many studies suggested that administration of rhGH at an early age can maximize the growth potential and support the overall well-being during childhood (18,19). The aim of this study was to evaluate the use of rhGH as a therapeutic agent for treatment of GHD children in Misurata following a year of therapy. One hundred seventy-four children with GHD were identified in our retrospective study. However, not every child identified in the study was included. There were only 50 child met the inclusion criteria of administrating rhGH therapy for a year. Challenges such as refusal to follow-up, parental ignorance of social and psychological impact of GHD disease, the availability and the expenses of the treatment may play a role in reducing the number of patients attending for follow up.

Gender distribution:

Among the 50 participants, 52% were males while (48%) were females. Although not statically different (P value >0.05) this is in agreement with a previous study in which the percentage of males were (64%) outnumbered the percentage of females (36%)(20). Lé ger, J., stated that boys have lower serum levels of growth hormone binding protein (GHBP) than girls before puberty (21), also some diseases can occur in males than females which could explain outnumbering of boys (22). Furthermore, Parents may perceive that short girls are more socially accepted than short boys although this may vary across different cultures and communities (23). Gender was not significantly related to the response to rhGH in this study. This finding is consistent with other larger studies investigating the response to rhGH therapy such as the Kolej international graduate studies index (KIGS) database (24).

Causes of growth hormone deficiency:

Table 1, shows the causes of GHD among the fifty participants. 70% of children had idiopathic GHD, 26% had genetic causes, and 4% had pituitary hypoplasia.

Table 1: Causes of GHD

Cause	No.	%
pituitary hypoplasia	2	4%
Genetic	13	26%
Idiopathic	35	70%

In consistent with a previous study in which patients with idiopathic GHD constitute almost two-thirds of the pathogenesis of GHD (70 %) (25) and 83 % of 208 patients were diagnosed with idiopathic GHD in a sample selected from the National Registry of GH Treatment of Children by the Dutch Growth Foundation (26). Also, out of 54,996 patients in the National Cooperative Growth Study (NCGS) registry between 1985 to 2006; idiopathic GHD represented the largest treated group (42%) (27).

Response to rhGH after one year of treatment:

In this study, the children age was between 4 and 12 years old (Table 2). The mean age before starting rhGH therapy was 6.74 years and the mean of initial height was 104.72 (Table 2). In addition, the mean difference in the growth rate for the patient was ΔHV = 5.163 cm/year after one year of rhGH therapy.

Forty-six patients (92%) met the criterion (Δ height >3 cm after one year of therapy).

Table 2: The age of children at initiation of therapy

The age at initiation therapy (years)	Age	No.	%
	4	5	10%
	5	8	16%
	6	2	4%
	7	14	28%
	8	6	12%
	9	9	18
	10	2	4%
	11	3	6%
	12	1	2%
	Total	50	100%

Growth response after one year of rhGH therapy administration is one of the best indicators of long-term height gain (28). In this study, most patients showed improvement in their growth rate (92%). These results were comparable to those of Alzahrani et al. (29) who studied the effect of use of rhGH on increasing the height of patients diagnosed with both idiopathic short stature (ISS) and idiopathic GH deficiency (IGHD). Alzahrani et al. found an increase in the height of participants after use of rhGH for one year regardless of the cause of the GHD; (the height gain in IGHD and ISS patients were 134.231±12.88, 134.04±10.90, respectively (29).

Age of diagnosis and response to treatment:

Unsatisfactory response to treatment was defined by the criteria: ΔHV acceleration of less than 3 cm/year from the pre-treatment growth rate. In the current study, patients were divided into groups according to treatment response: poor responders (ΔHV < 3 cm/year) and good responders (ΔHV ≥ 3 cm/year). The total number of children meeting the criteria as a good responder after a year of treatment was 92% (46/50). The percentage according to their ages, 93% (14/15) were 4-6 years old, 93.1% (27/29) were 7-9 years and 83% (5/6) were 10-12 years (figure 3). .

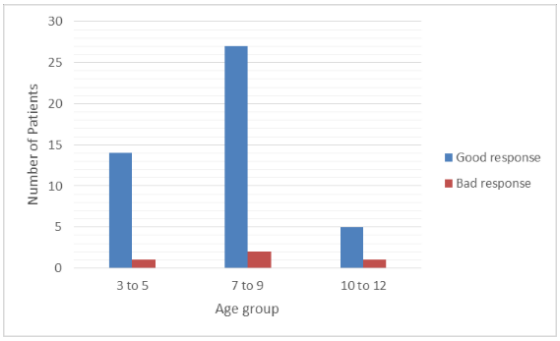

Figure 3: Age of diagnosis and response to treatment

It has been shown that total gain in height correlates significantly with younger age at the start of treatment in GHD (3,16,30). Therefore, the Growth Hormone Research Society advises that treatment should be initiated as soon as the diagnosis is made although no specific optimal time was specified for children diagnosed with GHD (1, 8, 31). In the current study, patients who began therapy at a younger age responded better to the treatment overall across all indications. Early age at start of therapy was identified as a predictor of adult height in children with ISS as well in other studies (16, 30, 32).

rhGH Dose (mg/kg/day)

The dose of rhGH treatment for 44 patients was 0.035 mg/kg/day, and for 6 patients was 0.045 mg/kg/day. The mean initial dose of rhGH was 0.0362 mg/kg/day and remained at same level throughout the observation period. A dose of 0.036 mg/kg/day (0.25 mg/kg/week) is recommended as the optimal initial dose (33). In order to achieve the optimum height velocity response, the dose of rhGH should be tailored according to GH responsiveness (34). In another study, the mean rhGH dose of GH treatment to treat IGHD

was (0.040 mg/kg/day) (35). The discrepancy in doses between studies may be due to differences in patient age, compliance, and the specific growth response being targeted (36-38).

Chronic disease:

Three children (6%) had confirmed type 2 diabetes after administration of rhGH. A review of the Kabi/Pfizer revealed that11 patients with type 1 diabetes, 18 patients with type 2 diabetes and 14 with impaired glucose tolerance (39). The National Cooperative Growth Study NCGS reported 22 children from a total of over 20.000 had developed diabetes while receiving GH therapy (40). After cessation of GH therapy 13 children still had diabetes, and 10 of these had existing risk factors for developing diabetes. It was concluded that in the absence of known risk factors, GH therapy during childhood and adolescence was unlikely to induce diabetes (39, 40).

In our study, chronic renal disease was detected in only one child (2%). The growth rate for the patient was 2.87 ($\Delta HV < 3$ cm/year) after one year of rhGH therapy. Growth failure is a common problem in children with chronic renal disease. Important factor which modifies GH responsiveness is the predominant chronic renal failure treatment that the patient is receiving (41). In addition, dialysis has a negative effect on GH efficacy because it can alter drug metabolism, protein binding and clearance rates (42).

Puberty state:

In 44 patients at the beginning of the therapy, puberty had not started yet (Tanner stage 1); one patient was classified as Tanner stage 2, four patients as stage 3 and one patient as stage 4 (table 3). The majority of cases (88%) in our study were prepubertal (Tanner stage 1), which is similar to the study of Miller et al (43). Strategies that combine rhGH treatment with suppression of puberty using GnRH analogs may result in improved height outcomes (44). Due to frequent delay in diagnosis of patients with short stature, rhGH treatment is often initiated close to, or even after, the start of the pubertal growth spurt. Studies have generally indicated that the growth response is greater if rhGH is started at a younger age, and particularly at the pre-pubertal stage, irrespective of the cause of short stature (45). While an increase in rhGH dose during puberty has been suggested, there are no clinical studies that have shown a convincing beneficial effect on adult height. Therefore, delaying puberty to allow exogenously administered rhGH to act for a longer period has been suggested as a strategy to improve overall linear growth. Oxandrolone administration has been examined in boys with constitutional delay of growth and idiopathic short stature, but had no significant effect on adult height (46). However, addition of oxandrolone to rhGH therapy has been studied in girls with Turner syndrome and provided approximately 3 cm of extra adult height gain (47).

Table 3: Frequency and percentages of patients at each pubertal stage

Frequency	Percent	
Tanner stage 1	44	88%
Tanner stage 2	1	2%
Tanner stage 3	4	8%
Tanner stage 4	1	2%
Total	50	100%

Conclusion

The aim of this study was to assess the efficacy of recombinant human growth hormone (rhGH) as a therapeutic intervention for one year treatment of children with GHD in Misurata. Data presented here suggested that the most common cause of GHD in our study

was idiopathic. In addition, the prevalence of GHD in males was more than that in females. Furthermore, it has been shown that the total gain in height was higher in children with younger age at start of the rhGH treatment; suggesting the importance of early intervention in treatment of GHD. Finally, the use of rhGH for one year has an effect on increasing the height of pediatric patients diagnosed with GHD. While our results were based on a small sample size and short period of follow-up, the findings reported here have provided insight into the GHD in Libyan children and the effectiveness of rhGH in increasing the height of children diagnosed with GHD.

Acknowledgments

The authors would like to thank staff at department of pediatric endocrinology in the Misrata Specialized Center for Diabetes and Endocrine for their assistance in granting access to the medical records.

References

1. P. C. Sizonenko *et al.*, Diagnosis and management of growth hormone deficiency in childhood and adolescence. Part 1: diagnosis of growth hormone deficiency. *Growth Horm IGF Res* **11**, 137-165 (2001).

2.M. B. Ranke, J. M. Wit, Growth hormone - past, present and future. *Nat Rev Endocrinol* **14**, 285-300 (2018).

3.D. Kelberman, K. Rizzoti, R. Lovell-Badge, I. C. Robinson, M. T. Dattani, Genetic regulation of pituitary gland development in human and mouse. *Endocr Rev* **30**, 790-829 (2009).

4.D. Le Roith, C. Bondy, S. Yakar, J. L. Liu, A. Butler, The somatomedin hypothesis: 2001. *Endocr Rev* **22**, 53-74 (2001).

5.P. D. Gluckman, M. M. Grumbach, S. L. Kaplan, The neuroendocrine regulation and function of growth hormone and prolactin in the mammalian fetus. *Endocr Rev* **2**, 363-395 (1981).

6.K. Albertsson-Wikland, S. Rosberg, Analyses of 24-hour growth hormone profiles in children: relation to growth. *J Clin Endocrinol Metab* **67**, 493-500 (1988).

7.P. C. Hindmarsh, D. R. Matthews, C. G. Brook, Growth hormone secretion in children determined by time series analysis. *Clin Endocrinol (Oxf)* **29**, 35-44 (1988).

8.J. Ayuk, M. C. Sheppard, Growth hormone and its disorders. *Postgrad Med J* **82**, 24-30 (2006).

9.L. S. Argetsinger, C. Carter-Su, Mechanism of signaling by growth hormone receptor. *Physiol Rev* **76**, 1089-1107 (1996).

10.J. Lillis, S. C. Hayes, K. Bunting, A. Masuda, Teaching acceptance and mindfulness to improve the lives of the obese: a preliminary test of a theoretical model. *Ann Behav Med* **37**, 58-69 (2009).

11.M. H. Zeller, A. C. Modi, Development and initial validation of an obesity-specific quality-of-life measure for children: sizing me up. *Obesity (Silver Spring)* **17**, 1171-1177 (2009).

12.R. Lindsay, M. Feldkamp, D. Harris, J. Robertson, M. Rallison, Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. *J Pediatr* **125**, 29-35 (1994).

13.G. V. Vimpani, A. F. Vimpani, S. J. Pocock, J. W. Farquhar, Differences in physical characteristics, perinatal histories, and social backgrounds between children with growth hormone deficiency and constitutional short stature. *Arch Dis Child* **56**, 922-928 (1981).

14.M. Dattani, M. Preece, Growth hormone deficiency and related disorders: insights into causation, diagnosis, and treatment. *Lancet* **363**, 1977-1987 (2004).

15.A. Takeda *et al.*, Recombinant human growth hormone for the treatment of

growth disorders in children: a systematic review and economic evaluation. *Health Technol Assess* **14**, 1-209, iii-iv (2010).

16.M. Thomas *et al.*, Prevalence and demographic features of childhood growth hormone deficiency in Belgium during the period 1986-2001. *Eur J Endocrinol* **151**, 67-72 (2004).

17.K. Stochholm *et al.*, Incidence of GH deficiency - a nationwide study. *Eur J Endocrinol* **155**, 61-71 (2006).

18.J. M. Wit, G. A. Kamp, B. Rikken, Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. *Pediatr Res* **39**, 295-302 (1996).

19.Y. Gao *et al.*, Effects of early recombinant human growth hormone treatment in young Chinese children with Prader-Willi syndrome. *Orphanet J Rare Dis* **18**, 25 (2023).

20.N. Salah, S. M. Abd El Dayem, L. Fawaz, M. Ibrahim, Predicting growth response among Egyptian prepubertal idiopathic isolated growth hormone deficient children. *J Pediatr Endocrinol Metab* **26**, 247-255 (2013).

21.J. Léger *et al.*, The relationship between the GH/IGF-I axis and serum markers of bone turnover metabolism in healthy children. *Eur J Endocrinol* **157**, 685-692 (2007).

22.A. Grimberg, E. Stewart, M. P. Wajnrajch, Gender of pediatric recombinant human growth hormone recipients in the United States and globally. *J Clin Endocrinol Metab* **93**, 2050-2056 (2008).

23.S. K. Lashari, H. B. Korejo, Y. M. Memon, To determine frequency of etiological factors in short statured patients presenting at an endocrine clinic of a tertiary care hospital. *Pak J Med Sci* **30**, 858-861 (2014).

24.F. Darendeliler, A. Lindberg, P. Wilton, Response to growth hormone treatment in isolated growth hormone deficiency versus multiple pituitary hormone deficiency. *Horm Res Paediatr* **76 Suppl 1**, 42-46 (2011).

25.P. Chatelain, Trends in the diagnosis and treatment of short stature as revealed by KIGS. *Growth hormone therapy in KIGS* **10**, 11-20 (1999).

26.M. A. de Ridder, T. Stijnen, A. C. Hokken-Koelega, Prediction of adult height in growth-hormone-treated children with growth hormone deficiency. *J Clin Endocrinol Metab* **92**, 925-931 (2007).

27.J. Bell *et al.*, Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab* **95**, 167-177 (2010).

28.M. Kim, E. Y. Kim, E. Y. Kim, C. H. So, C. J. Kim, Investigating whether serum IGF-1 and IGFBP-3 levels reflect the height outcome in prepubertal children upon rhGH therapy: LG growth study database. *PLoS One* **16**, e0259287 (2021).

29.A. K. Alzahrani *et al.*, Differences in Response to Recombinant Growth Hormone Therapy on Height Gain in Patients with Idiopathic Short Stature Vs. Patients with Growth Hormone Deficiency. *Cureus* **12**, e7319 (2020).

30.K. S. Alatzoglou, M. T. Dattani, Phenotype-genotype correlations in congenital isolated growth hormone deficiency (IGHD). *Indian J Pediatr* **79**, 99-106 (2012).

31.V. Petkovic *et al.*, Short stature in two siblings heterozygous for a novel bioinactive GH mutant (GH-P59S) suggesting that the mutant also affects secretion of the wild-type GH. *Eur J Endocrinol* **168**, K35-43 (2013).

32.T. A. Fleisher *et al.*, X-linked hypogammaglobulinemia and isolated growth hormone deficiency. *N Engl J Med* **302**, 1429-1434 (1980).

33.M. Thorner, M. Vance, Growth hormone, 1988. *The Journal of Clinical Investigation* **82**, 745-747 (1988).
34.P. G. Murray, P. E. Clayton, Disorders of growth hormone in childhood. (2015).
35.B. A. Bengtsson *et al.*, The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. *J Clin Endocrinol Metab* **84**, 3929-3935 (1999).
36.G. Amato *et al.*, Recombinant growth hormone (GH) therapy in GH-deficient adults: a long-term controlled study on daily versus thrice weekly injections. *J Clin Endocrinol Metab* **85**, 3720-3725 (2000).
37.N. Mauras, K. M. Attie, E. O. Reiter, P. Saenger, J. Baptista, High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group. *J Clin Endocrinol Metab* **85**, 3653-3660 (2000).
38.Y. Xue, Y. Gao, S. Wang, P. Wang, An examination of the effects of different doses of recombinant human growth hormone on children with growth hormone deficiency. *Exp Ther Med* **11**, 1647-1652 (2016).
39.W. S. Cutfield *et al.*, Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *The Lancet* **355**, 610-613 (2000).
40.S. L. Blethen *et al.*, Safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study experience. *The Journal of Clinical Endocrinology & Metabolism* **81**, 1704-1710 (1996).
41.J. Karlberg *et al.*, Early age-dependent growth impairment in chronic renal failure. *Pediatric Nephrology* **10**, 283-287 (1996).
42.E. Wühl *et al.*, Short dialyzed children respond less to growth hormone than patients prior to dialysis. *Pediatric Nephrology* **10**, 294-298 (1996).
43.B. S. Miller, K. Sarafoglou, O. Y. Addo, Development of Tanner stage–age adjusted CDC height curves for research and clinical applications. *Journal of the Endocrine Society* **4**, bvaa098 (2020).
44.T. R. Smith, J. S. Elmendorf, T. S. David, J. Turinsky, Growth hormone-induced insulin resistance: role of the insulin receptor, IRS-1, GLUT-1, and GLUT-4. *American Journal of Physiology-Endocrinology and Metabolism* **272**, E1071-E1079 (1997).
45.P. A. Lee *et al.*, Comparison of response to 2-years' growth hormone treatment in children with isolated growth hormone deficiency, born small for gestational age, idiopathic short stature, or multiple pituitary hormone deficiency: combined results from two large observational studies. *International journal of pediatric endocrinology* **2012**, 1-8 (2012).
46.J. M. Wit, W. Oostdijk, Novel approaches to short stature therapy. *Best Pract Res Clin Endocrinol Metab* **29**, 353-366 (2015).
47.T. C. Sas *et al.*, Safety and efficacy of oxandrolone in growth hormone-treated girls with Turner syndrome: evidence from recent studies and recommendations for use. *Horm Res Paediatr* **81**, 289-297 (2014).