Chapter 7

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Current Indications for Growth Hormone Therapy for Children and Adolescents

Erick Richmond[a] · Alan D. Rogol[b]

[a]Pediatric Endocrinology, National Children's Hospital, San José, Costa Rica; [b]Pediatric Endocrinology, Riley Hospital, Indiana University School of Medicine, Indianapolis, Ind., and University of Virginia, Charlottesville, Va., USA

Abstract

Growth hormone (GH) therapy has been appropriate for severely GH-deficient children and adolescents since the 1960s. Use for other conditions for which short stature was a component could not be seriously considered because of the small supply of human pituitary-derived hormone. That state changed remarkably in the mid-1980s because of Creutzfeldt-Jakob disease associated with human pituitary tissue-derived hGH and the development of a (nearly) unlimited supply of recombinant, 22 kDa (r)hGH. The latter permitted all GH-deficient children to have access to treatment and one could design trials using rhGH to increase adult height in infants, children and adolescents with causes of short stature other than GH deficiency, as well as trials in adult GH-deficient men and women. Approved indications (US Food and Drug Administration) include: GH deficiency, chronic kidney disease, Turner syndrome, small-for-gestational age with failure to catch up to the normal height percentiles, Prader-Willi syndrome, idiopathic short stature, SHOX gene haploinsufficiency and Noonan syndrome (current to October 2008). The most common efficacy outcome in children is an increase in height velocity, although rhGH may prevent hypoglycemia in some infants with congenital hypopituitarism and increase the lean/fat ratio in most children – especially those with severe GH deficiency or Prader-Willi syndrome. Doses for adults, which affect body composition and health-related quality of life, are much lower than those for children, per kilogram of lean body mass. The safety profile is quite favorable with a small, but significant, incidence of raised intracranial pressure, scoliosis, muscle and joint discomfort, including slipped capital femoral epiphysis. The approval of rhGH therapy for short, non-GH-deficient children has validated the notion of GH sensitivity, which gives the opportunity to some children with significant short stature, but with normal stimulated GH test results, to benefit from rhGH therapy and perhaps attain an adult height within the normal range and appropriate for their mid-parental target height (genetic potential).

Introduction

Human growth hormone (hGH) is a single-chain, 191-amino-acid protein of 22 kDa molecular weight. It is synthesized, stored and released from the somatotropes of the anterior pituitary gland. Multiple additional molecular variants, including a 20-kDa form produced by the gene deletion of 14 amino acids and other post-translational isoforms, for example glycosylated and sulfated forms, of unknown physiological significance exist within the systemic circulation [1].

GH is relatively species-specific since only primate GH has efficacy in the human [2, 3]. None of the small trials with animal GH or enzymatically-produced fragments from animal GH showed growth-promoting efficacy in the human [4].

hGH was first extracted in the late 1940s [5] and administered to humans beginning in 1958 [6, 7]. Treatment of both children and adults was reported in that first clinical trial, although the latter took a number of years for confirmation of efficacy since so little hormone was available (essentially one pituitary per child per day). Thus, in the early years only profoundly GH-deficient children received treatment. Much of the time so little hormone was available that many children were treated 6 or 9 months a year permitting other, equally needy, children to reap some benefit from hGH therapy.

That all changed in the early 1980s when it became clear that Creutzfeldt-Jakob disease could be transmitted by human brain tissue and recombinant (r)hGH became available [8]. At that time a seemingly endless supply of the pure 22-kDa hormone permitted all GH-deficient children to have access to treatment and one could now design trials using rhGH to increase adult height in infants, children and adolescents with causes of short stature other than GH deficiency, as well as trials in adult GH-deficient men and women. The next 20 years led to at least 7 additional indications in children and 3 new ones in adults (table 1).

hGH is administered to promote linear growth in short children. The following are the US Food and Drug Administration (FDA)-approved indications for GH (current to October 2008) and in parentheses the indications approved in Europe (E) by the European Agency for the Evaluation of Medicinal Products (EMEA).

The most common efficacy outcome in infants, children and adolescents is an increase in linear growth, although rhGH may prevent hypoglycemia in some infants with congenital hypopituitarism and increase the lean/fat ratio in children with the Prader-Willi syndrome (see below).

The dose-response curve for height gain versus dose of rhGH (log scale) is rather flat in those with GH deficiency [9], even through the much higher doses (including 100 μg/kg/day) administered more recently [10]. The dose for adults which effects body composition and health-related quality of life are much lower per kilogram of body mass.

Table 1. Approved indications for GH therapy in children and adults in the USA and Europe (E)

Children
Growth hormone deficiency (E)
Chronic kidney disease (E)
Turner syndrome (E)
Small-for-gestational age infants who fail to catch up to the normal growth percentiles (E)
Prader-Willi syndrome (E)
Idiopathic short stature
SHOX gene haploinsufficiency (E)
Noonan syndrome
Adults
Growth hormone deficiency (E)
HIV/AIDS wasting
Short bowel syndrome

In this review, the studies that were selected for analysis were mainly randomized controlled studies, with the larger number of patients and the longest treatment duration of the available publications.

Growth Hormone Deficiency (GHD)

The administration of GH to treat children with sort stature resulting from GHD or GH insufficiency has now accrued over 40 years of clinical experience. In 1985, the US FDA approved the use of rhGH for the treatment of GHD and remains the primary indication for GH treatment in childhood. GHD is fundamentally a clinical diagnosis, based upon auxologic features. Assessment of laboratory tests, whether static, for example the measurement of IGF-1 and IGFBP-3, or dynamic, for example, secretagogue-stimulated GH secretion is confirmatory [11]. Radiologic evaluation of the hypothalamus and pituitary (CT scan or MRI) is helpful in patients with suspected congenital GHD or to detect space-occupying lesions (see Chapters 1 and 3 for fuller discussion of these points).

The primary objectives of therapy of GHD are normalization of height during childhood and attainment of adult height within the normal range. The greater efficacy demonstrated in recent large international databases [12, 13] compared with the initial studies of GH treatment in GHD patients (table 2) probably reflects the combined effects of the higher GH dose, the more physiologic injection frequency, and the younger age at initiation of treatment. Current consensus guidelines recommend a dose in the range of 0.025–0.05 mg/kg/day [21, 22]. Under

Table 2. GH trials in children with GHD

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
88	8.2	–2.9	0.023–0.030*	9.9	2.4	14
121	10.8	–3.2	0.043*	7.8	2.5	15
1,034	12.2	–2.8	0.028–0.043*	4.6	1.3	16
932	12.0	–2.8	NA	4.9	1.0	17
25	10.0	–4.5	0.020–0.028*	8.6	1.1	18
18	12.0	–5.6	0.020–0.023	6.2	2.8	19
13	3.6	–4.1	0.023–0.031*	12.2	3.2	20

NA = Not available.
* GH dose was administered 3–7 times per week.

special circumstances, higher doses may be required, including adolescents with late diagnosis and diminished period of time for catch-up growth [23]. Recently it has been proposed that IGF-1-based GH dosing may improve growth responses, although at higher average GH doses [24].

Significant side effects of GH treatment in children are uncommon. These include benign intracranial hypertension, prepubertal gynecomastia, arthralgia, and edema [21, 22]. Management of these side effects may include either transient reduction of dosage or temporary discontinuation of GH. In the absence of other risk factors, there is no evidence that the risk of leukemia, brain tumor recurrence, slipped capital femoral epiphysis or diabetes are increased in recipients of long-term GH treatment.

GHD may or not persist into adulthood. After the attainment of adult height, retesting of the GH-IGF-1 axis is recommended prior to the decision to continue or not with GH treatment through adulthood [25]. GH has major metabolic actions, which are important for body composition and health in adults as well as in children.

Chronic Renal Insufficiency (CRI), also Known as Chronic Kidney Disease (CKD)

Growth failure is common in children with CRI, which was the first non-GHD growth disorder for which GH was approved for use by the US FDA in 1993 and by the EMEA in 1995.

Malnutrition and alterations in the GH-IGF axis seem to be the most frequent and most important factors contributing to the degree of growth disturbance. Other factors are: the specific etiology of the renal disease, acid-base disturbances,

Table 3. GH trials in children with CRI

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
38	10.4	–3.1	0.047	5.3	1.4	31
183	8.2	–2.7	0.027–0.054	5.3	0.4	32
45	7.8	–3.0	0.050	8.0	2.6	33
30	5.6	–2.7	0.050	1.0	0.8	34
55	6.0	–2.9	0.050	2.0	1.4	35

* GH dose was administered 3–7 times per week.

secondary hyperparathyroidism, age, duration of renal disease and treatment modalities [26]. Long-term treatment with high-dose glucocorticoids in children leads to growth failure and protein catabolism and glucocorticoids interfere with the integrity of the GH-IGF axis at various levels [27].

Children with CRI who do not receive GH treatment attain an adult height below the expected genetic potential in the majority and below –2 SDS in about half of affected individuals [28]. Approval of GH treatment in patients with growth failure associated with CRI was based on only short-term data, but subsequent studies showed that GH has some short-term effect although adult height are perhaps less impressive [29, 30–35] (table 3). GH treatment is approved only for CRI before renal transplantation, but a number of studies have successfully treated children after transplantation [36, 37].

Although GH treatment in patients with CRI is considered safe [38], some studies have raised the possibility of deterioration of renal function, especially in those who have a previous history of renal graft rejection [39], and alterations in glucose metabolism [40]. Careful monitoring is recommended, especially in children who have a family history of diabetes or those receiving concomitant glucocorticoid therapy.

Turner Syndrome (TS)

TS occurs in approximately 1 in every 2,500 live-born females, making it one of the most common chromosomal disorders [41]. The diagnosis of TS requires the presence of characteristic physical findings [42, 43] in addition to a complete or partial absence of the second sex chromosome, with or without cell line mosaicism [44]. Untreated adult women with TS achieve an average adult height 20 cm shorter than their mid-parental (target) height [45, 46].

Table 4. GH trials in girls with TS

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
70	9.3	–3.2	0.054*	7.6	1.1	49
60	9.5	–3.0	0.050	5.9	1.0	50
232	9.7	–3.1	0.039–0.051	5.5	1.1	51
154	10.3	–3.2	0.050	5.7	1.1	52
14	10.6	–3.2	0.037–0.111	4.0	1.1	53
68	6.6	–2.8	0.045–0.090	8.6	1.7	54
188	11.7	–3.7	0.025–0.056	2.4	0.9	55
704	11.9	–3.4	0.043	5.0	1.2	56
88	2.0	–1.4	0.050	2.0	1.1	57
60	10.9	–2.7	0.047	6.8	0.9	58

* GH dose was 0.125 mg/kg three times per week.

Despite some evidence for subtle alterations in IGF-1 physiology, the growth deficit in individuals with TS is believed to result mainly from haploinsufficiency of one copy of the SHOX gene, located within the pseudoautosomal region on the distal short arm of the X (and Y) chromosome [47], and discussed in further detail in the section on SHOX deficiency (see below).

Despite dozens of publications of GH treatment in TS patients over the last two decades, a recent Cochrane Center review identified only four studies in which GH treatment was compared in a randomized fashion with a concurrent non-treatment or placebo control [48]. In these studies, patients treated to adult or near-adult height achieved average height gains ranging from about 5 to 8 cm over periods of treatment ranging from 5.5 to 7.6 years, and the doses varied between 0.039 and 0.054 mg/kg/day (table 4) [49–52]. Other studies of GH treatment in TS patients have variable results probably due to differences in methodology with respect to patient selection, the type of controls used, rhGH dose and frequency, concomitant treatment with oxandrolone or estrogen and analytic methods (table 4) [53–58].

Pediatric and adolescent patients with TS appear to be at increased risk for some adverse events associated with GH treatment, including intracranial hypertension, scoliosis, pancreatitis, and slipped capital femoral epiphysis, compared with other populations who receive GH treatment [59]. They are also at risk for events known to be associated with TS, including autoimmune disorders, and likely type 1 diabetes mellitus, as well as hearing loss, hypertension and aortic dissection with rupture [60, 61].

Children Born Small-for-Gestational Age (SGA), Who Fail to Catch Up to the Normal Growth Channels

The definition of SGA varies in the pediatric literature. A recent consensus statement recommended that SGA should be defined as a weight and/or length less than –2 SD for the length of pregnancy [62]. Babies can then be subclassified into SGA for weight, SGA for length, or SGA for both weight and length [63], although the response to rhGH therapy did not differ between these groups treated in a trial of 201 SGA babies in the Netherlands [64]. Approximately 90% of infants born SGA undergo spontaneous catch-up growth to return to their genetic potential by the end of the second year of life; however, most catch up occurs by 9–15 months The preterm infant may take 4 years (rarely more) to achieve a height within the normal range [65], the remaining 10% who do not catch up are eligible for rhGH therapy.

The activity of the GH-IGF-1 at birth or during the first weeks of life is not predictive of later growth, and in most patients the endocrine evaluation of growth is not helpful [66]. Later assessment of the GH-IGF-1 axis in the short SGA child may be required if growth velocity is persistently reduced and/or if signs of GH deficiency or hypopituitarism are present [67].

Treatment with rhGH is indicated only when other causes of short stature, including medications that effect growth, chronic diseases, endocrine disorders or syndromes associated with diminished growth and GH therapy is not recommended, have been ruled out.

Experience with the use of rhGH therapy in SGA children started more than three decades ago [68, 69]. The US FDA approved in 2001 the use of GH for the long-term treatment of growth failure in children born SGA, who fail to catch up to the normal growth channels by age 2 years. The recommendation is to administer a dose of up to 0.07 mg/kg/day. In contrast, the EMEA approved GH in 2003 for the treatment of children born SGA after the age of 4 years at a dose of 0.033 mg/kg/day. The reason for waiting until age 4 years is that there is a small possibility of spontaneous catch-up growth between 2 and 4 years of age, especially in those children born prematurely [70].

There is considerable variation in the height gain attained with rhGH therapy in children born SGA, even after adjusting for differences in parental height, age at start of treatment, and duration of treatment [71]. Data from recent randomized rhGH trials in short children born SGA are presented in table 5 [72–75].

The effect of GH on glucose metabolism in children born SGA is of potential concern. Although there is evidence of a tendency to develop higher fasting plasma insulin concentrations and relative insulin resistance during rhGH treatment [76], that phenomenon typically resolves after discontinuation of rhGH treatment [77] although he patients still remain hyperinsulinemic as they are pre-intervention.

Table 5. Randomized GH trials in short children born SGA

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
28	5.4	–3.6	0.033–0.067	10.0	1.2	72
77	10.7	–2.8	0.033	7.0	1.3	73
91	12.7	–3.2	0.067	2.7	0.6	74
54	8.1	–3.0	0.033–0.067	7.8	1.8	75

Table 6. GH trials in children with PWS

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
35	9.9	–1.1	0.026–0.043	2	0.8	83
15	6.8	–1.6	0.037	1	1.2	84
22	6.9	–1.6	0.030–0.060	9.2	1.9	85
44	4.5	–2.1	0.026–0.043	2	1.6	86

Adverse events due to rhGH therapy are not more common in this population than in other conditions treated with rhGH [78].

Prader-Willi Syndrome (PWS)

PWS, a genetic disorder first described in 1956, is caused by deletion or lack of expression of a portion of the paternally derived chromosome 15 [79]. Effected children are characterized by obesity, hypotonia, short stature, hypogonadism and behavioral abnormalities [80]. Body composition abnormalities including increased fat mass, decreased lean body mass, and low bone density have been demonstrated in patients with PWS [81]. The estimated incidence of this condition is of 1 in 10,000–12,000 births and is the most common of all the syndromes associated with severe obesity [82].

The efficacy of rhGH to increase linear growth and to improve body composition measurements in genetically confirmed patients with PWS irrespective of their GH status is well documented [83–86] (table 6). In 2000 the US FDA approved the use of rhGH for pediatric patients who have growth failure due to PWS and European labeling states 'for improvement of growth and body composition'.

Sudden death has been reported in 17 children with PWS who were treated with rhGH. These children had underlying morbid obesity and respiratory, or possible sleep disorders [87]. Cause and effect remain to be established. Nonetheless, in patients with PWS, correction of underlying airway obstruction and sleep studies should be considered before initiation of rhGH therapy [88]. Because weight gain is a major problem in PWS and the risk of type 2 diabetes is increased, careful monitoring of glucose metabolism is mandatory when rhGH is prescribed [89].

Idiopathic Short Stature (ISS)

ISS or non-GH-deficient short stature, perhaps the most controversial of all the conditions in which rhGH therapy is used, has been approved in the USA. ISS refers to a heterogeneous group of children whose short stature cannot be explained by a defined pathologic process. The diagnosis is based on a process of exclusion, because patients with ISS have no distinguishing clinical or phenotypic features. Most children have a height that is only slightly below the normal range, but others have growth failure as significant as that of GH deficiency [90]. As molecular diagnostic methodology has become more sophisticated, and as new growth-related genes have been discovered, some children with apparent ISS have specific defects in one of many genes along the GH-IGF-1 axis (see Chapter 3).

In 2003 the US FDA approved the administration of GH for children with ISS and height SDS ≤2.25. Although the USA is the only country that has approved the use of GH in ISS, there had been prior longstanding use of this treatment in an off-label fashion in children who had unexplained short stature in many countries, including the USA.

A number of meta-analyses have reviewed the efficacy of rhGH treatment in children with ISS, such studies suggest average height gains between 3 and 7 cm [91, 92]. As with all rhGH treatment indications, responses vary among patients (table 7) [92–97]. In GH trials with children with ISS reported to date, small sample sizes remain a major problem, as well as the relatively high percentage of drop-outs of non-responders in studies with longer duration of treatment.

Data from large databases and long-term GH postmarketing studies indicate that rates of adverse events are slightly lower, but not statistically significantly different, in this patient group than in other rhGH-treated patients [98, 99].

SHOX Gene Haploinsufficiency (SHOX)

The SHOX gene is located in the pseudoautosomal regions at the distal ends of the X and Y chromosomes, this gene encodes a homeodomain transcription

Table 7. GH trials in children with ISS

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
68	12.5	–2.7	0.031*	4.4	0.5	93
50	10.1	–3.2	0.035–0.053	6.5	0.8	94
80	10.1	–2.7	0.043	5.7	0.7	95
29	7.8	–2.1	0.039–0.078	8.0	1.0	96
126	11.5	–2.7	0.033–0.067	5.9	1.3	97

* GH dose was 0.074 mg/kg three times per week.

Table 8. GH trials in children with SHOX gene haploinsufficiency

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
27	7.3	–3.3	0.050	2.0	0.9	105

factor responsible for a significant proportion of long bone growth [100]. SHOX haploinsufficiency is the primary cause of short stature in TS and Leri-Weill dyschondrosteosis and in 2% to 3% of patients with ISS [101]. The prevalence of this condition is estimated to be approximately 1 in 2500 individuals [101]. Without GH treatment the estimated average adult height of patients with SHOX deficiency is estimated to be –2.3 SDS for females and –1.8 SDS for males [102].

Soon after the discovery of the SHOX gene, experience with rhGH started in patients with Leri-Weill dyschondrosteosis and those with non-syndromic SHOX deficiency, but published studies are mostly case reports or small non-controlled trials [103, 104]. The only randomized controlled trial is summarized in table 8 [105].

Despite the little experience with GH treatment of patients with SHOX gene haploinsufficiency, it appears to have a safety profile comparable to that reported in other pediatric indications for which GH has been previously approved.

Noonan Syndrome (NS)

NS is a relatively common multiple congenital anomaly syndrome characterized by typical facial features, short stature and congenital heart defects [106]. The

Table 9. GH trials in children with NS

Patients n	Mean age at start, years	Mean height SD at start	GH dose mg/kg/day	Mean duration of treatment years	Estimated height gain SD	Ref.
18	8.2	–2.9	0.033–0.066	7.5	1.7	111
24	7	–3.2	0.025–0.11	7.6	0.6	112
29	11	–2.7	0.050	6.4	1.3	113

incidence is estimated to be approximately 1/1,000 to 1/2,500 live births, males and females are affected equally and their karyotypes are normal. The inheritance of NS is autosomal dominant with variability in expression [107]. The molecular biology of NS is discussed in Chapter 3.

Short stature is one of the cardinal features of NS; length at birth is within the normal reference range, but during childhood, effected children grow at a slow rate and the median adult height is reported to be below –2 SDS (162.5 cm in men and 152.7 cm in women) [108]. Specific growth charts have been developed for individuals with NS [109]. The underlying cause of short stature is unknown, but pathology in the GH/IGF-1 axis has been reported and similar to patients with TS, decreased hGH sensitivity has been hypothesized [110].

Over the last two decades, few rhGH treatment trials in children with NS have been reported and fewer data presented of near-adult or adult height. The most important trials in which adult height or near-adult height data are reported are summarized in table 9 [111–113].

Studies have demonstrated that rates of adverse events are not different in this patient group than in other GH-treated patients. Although special attention should be paid to cardiac function and regular echocardiograms are recommended, recent studies have shown no changes in cardiac dimensions [114].

Conclusions

The administration of GH to treat children with sort stature resulting from GHD or GH insufficiency has now accrued over 40 years of clinical experience. The use of rhGH for the treatment of GHD remains the primary indication for GH treatment in childhood, but 7 more indications have been approved over the last years.

In all the conditions discussed GH has been shown to increase height velocity leading to progressive normalization of height SDS during childhood and in GHD, TS and ISS, there is some evidence of improvement in adult height.

Even though in theses conditions rhGH therapy is considered effective in terms of growth and with a good safety profile, additional considerations are needed to responsibly assess the long-term value of the added height increment and to balance expected benefit with economical considerations. The approvals of rhGH therapy for short non-GHD children has validated the notion of GH sensitivity, which gives the opportunity to some children with significant short stature but with normal GH test results to benefit from rhGH and perhaps attain an adult height within the normal range.

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Alan D. Rogol, MD, PhD
Department of Pediatrics, University of Virginia
685 Explorers Rd, Charlottesville, VA 22911-8441 (USA)
Tel. +1 804 971 6687, Fax +1 804 971 1147
E-Mail adrogol@comcast.net