

Specialty Drugs for the Treatment of Short Stature in Children— Pros, Cons, and Perspectives for the Future

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DOI: 10.17925/USE.2010.06.1.78

Abstract

Specialty drugs are generally defined as medications that involve special drug handling and/or parenteral administration and are typically used to treat complex medical conditions. They are typically biologicals, often very expensive, and generally prescribed by specialists. The recent surge in use of specialty pharmaceuticals has placed these drugs in the spotlight as policy-makers struggle to contain healthcare costs. Specialty drugs are central to discussions about optimal ways to manage childhood short stature; recombinant human growth hormone (rhGH) and recombinant human insulin-like growth factor-1 (rhIGF-1)—specialty drugs with annual prices of \$20,000 to \$30,000 per child—are available to treat childhood short stature from specific causes. rhGH and rhIGF-1 revolutionized treatment of severe short stature resulting from growth hormone deficiency and growth hormone insensitivity, respectively. Over the past 20 years, use of rhGH has expanded to other conditions. Expanded use of the newer rhIGF-1 may occur in an analogous manner. This article reviews the background, current status, and potential for these drugs in view of current evidence and policies.

Keywords

Growth hormone (GH), insulin-like growth factor-1 (IGF-1), specialty drugs, biologicals, short stature

Disclosure: The authors have no conflicts of interest to declare.

Acknowledgement: This work was supported in part by grants from the NIH and an award by the Rainbow Babies and Children's Hospital Foundation.

Received: October 1, 2010 **Accepted:** November 5, 2010 **Citation:** *US Endocrinology*, 2010;6:78–83

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Specialty Drugs— Evolving Terminology and Context

Historically, specialty drugs were loosely defined as pharmaceutical products requiring specialized services such as special handling and refrigeration, skilled administration via injection or infusion, and comprehensive patient education to support proper use; these services often translated into higher cost.¹ Many were biological drugs (large molecule drugs produced by genetic or protein engineering rather than via chemical reaction as with traditional small molecule drugs). Sometimes the terms specialty drugs and biologicals have been used interchangeably.^{2,3} Specialty drugs were originally used in relatively rare, complex medical conditions affecting small numbers of patients. However, the number of specialty pharmaceuticals has grown exponentially and new drugs are becoming available to treat conditions that affect larger populations. This explosion reflects the success of the biopharmaceutical industry. Over 200 specialty drugs are currently available and more than 500 are in clinical development, a dramatic increase from 15 years ago when fewer than 30 such drugs existed.^{1,4} Because of the rising number of these medications, many insurers have begun to revise their tiered drug-copayment structures to include a higher 'specialty' tier requiring higher cost-sharing by patients for

particularly expensive drugs.⁵ As a result, the term 'specialty drug' has come to be defined by price. The Centers for Medicare and Medicaid Services currently defines specialty drugs as medications that cost more than \$600 for a one-month supply.⁶

The surge in specialty pharmaceutical development and use has placed these drugs in the spotlight as policy-makers struggle to contain healthcare costs. Specialty drugs are now the fastest-growing segment of drug spending.⁷ While non-specialty drugs have annual spending increases of 2–6%, specialty drug costs are increasing by 10% or more, annually. If current trends continue, by 2030, specialty pharmacy costs will exceed \$1 trillion a year.¹ Given current concerns about the financial sustainability of US healthcare⁸ and recognizing typical specialty drug prices of \$6,000 to over \$400,000 per year,⁷ policy-makers, the medical community, and society should address how to apply these drugs to ensure appropriate use, optimal access, and greatest value.

Specialty Drugs and Short Stature

Childhood growth is controlled by many factors. Normal growth requires an intact growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis. GH is secreted from the anterior pituitary and binds its specific cell surface

receptor to induce effects, including synthesis of IGF-1. Both GH and IGF-1 act at the growth plate to stimulate statural growth. Other major determinants of linear growth in childhood are thyroid hormone, nutritional status, specific genes, and familial potential. The sex steroids testosterone and estrogen also play a role in childhood growth by promoting the pubertal growth spurt and eventually causing fusion of the growth plate and cessation of statural growth. Thus, short stature in children can arise from many causes including GH deficiency, GH insensitivity, other endocrine disorders, systemic disease, nutritional deficiencies, specific genetic defects, and familial predisposition. The term idiopathic short stature (ISS) is applied to short children (with heights two or more standard deviations below the mean for age) in whom no disease can be identified. Despite controversy, this definition, based primarily on height standard deviation scores, includes children with familial short stature and those with constitutional delay in growth and development,⁹ conditions not traditionally considered to be diseases.

Currently two specialty drugs—recombinant human GH (rhGH) and recombinant human IGF-1 (rhIGF-1)—are available to treat childhood short stature. Additionally, the specialty drug leuprolide, a gonadotrophin-releasing hormone (GnRH) agonist, traditionally used in pediatric patients to treat precocious puberty, could potentially be used to delay the onset of puberty in short children in order to allow for prolonged statural growth before growth plate fusion.

The US Food and Drug Administration (FDA) first approved rhGH in 1985 for treatment of childhood GH deficiency (estimated US prevalence 1 in 3,500¹⁰). Before that, GH derived from cadaveric pituitary glands presented the only therapeutic option for GH-deficient children. Treatment with cadaveric GH was problematic because of limited supply (leading to sub-optimal GH dosing and average final height often more than two standard deviations below the mean) and ultimately cadaveric GH was withdrawn because some recipients developed Creutzfeldt-Jakob disease.^{11,12} rhGH revolutionized treatment of GH deficiency by providing a potentially limitless supply of therapy and eliminating the risk of Creutzfeldt-Jakob disease transmitted via human tissue. Over the following 25 years, rhGH gained successive FDA approvals for a number of conditions characterized by short stature, including chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, being born small for gestational age (SGA), ISS, short stature homeobox-containing gene (SHOX) deficiency, and Noonan syndrome (see *Table 1*).¹³ Although most of these conditions do not involve GH deficiency, GH treatment can increase growth, presumably by providing more GH than the apparently normal endogenous amounts. The largest group of children eligible for rhGH treatment are those with ISS; the FDA approval for ISS specifies that candidates have height standard deviation score more than 2.25 below the mean (and growth rate unlikely to permit attainment of adult height in the normal range). Approximately 500,000 US children have heights below this threshold. Thus, if all eligible children (based on degree of short stature) were considered for rhGH treatment, which costs approximately \$20,000 per child per year, potential annual cost would exceed \$10 billion.¹⁴

Human IGF-1 was cloned in 1983 and synthesized by recombinant DNA technology in 1986. Clinical trials of rhIGF-1 in patients with GH insensitivity from GH receptor or post-receptor defects followed shortly

Table 1: Year of US Food and Drug Approval and Indicated Uses for Recombinant Human Growth Hormone and Recombinant Human Insulin-Like Growth Factor-I

Recombinant Human Growth Hormone	
Year of rhGH FDA approval	Indication
1985	GH deficiency
1993	Chronic renal insufficiency
1996	Turner syndrome
1997	Adult GH deficiency
2000	Prader-Willi syndrome
2001	Small for gestational age (and failure to manifest catch-up growth by 2–4 years)
2003	Idiopathic short stature
2003	Short bowel syndrome in patients receiving specialized nutritional support (no pediatric studies when approved)
2003	HIV patients with wasting or cachexia (adults)
2006	SHOX deficiency
2007	Noonan syndrome
Recombinant Human Insulin-Like Growth Factor-I	
Year of rhIGF-1 FDA approval	Indication
2005	Severe primary IGF-1 deficiency or GH gene deletion with development of neutralizing antibodies to GH

rhGH = recombinant human growth hormone; rhIGF-1 = recombinant human insulin-like growth factor-I.

thereafter, ultimately demonstrating acceleration of growth by rhIGF-1 in these rare conditions that do not respond to GH therapy. Based on the results of these trials, the FDA approved rhIGF-1 in 2005 for the orphan indication of severe primary IGF-1 deficiency or GH gene deletion with development of neutralizing antibodies to GH (see *Table 1*). Severe IGF-1 deficiency was defined by height more than three standard deviations below the mean, IGF-1 scores more than three standard deviations below the mean, and normal or elevated GH levels. Severe IGF-1 deficiency was noted to include patients with GH receptor or post-receptor mutations and IGF-1 gene defects.¹⁵

Commercial availability of rhIGF-1 has added to the arsenal of agents that can potentially be used to treat children with short stature. Although currently of unproven long-term efficacy in conditions other than the orphan indication discussed above, the availability of rhIGF-1 has opened the door to its possible use in other conditions with less severe deficiency of IGF-1 and, in theory, perhaps even in children with ISS. At an annual rhIGF-1 cost of approximately \$30,000 per child, the financial impact of expanded rhIGF-1 use could be enormous.¹³ In fact, in a report to the US Securities and Exchange Commission, the manufacturer of rhIGF-1 projected a \$200 million annual market in the US and Western Europe for an estimated 24,000 children with severe primary IGF-1 deficiency, or a \$1 billion annual market for an estimated 60,000 children with (non-severe) primary IGF-1 deficiency.¹⁶ The use of the term primary IGF-1 deficiency in this manner has been criticized as representing a departure from conventional classification schemes of growth disorders in which the term ‘primary IGF-1 deficiency’ refers to rare congenital or genetic defects leading to IGF-1 deficiency, and has led to new controversy regarding the nomenclature of disturbances of the GH-IGF-1 axis.^{16–18}

Pros and Cons of Specialty Drugs for Short Stature

Weighing the pros and cons of rhGH and rhIGF-1 therapy requires analysis of many factors, including efficacy of treatment in improving final height, metabolic parameters, psychosocial functioning, safety, ethical considerations, financial cost, and other burdens of therapy.

Recombinant Human Growth Hormone Height Attainment

The use of rhGH therapy effectively increases final height in GH deficiency and several other conditions associated with childhood short stature. In children with classical GH deficiency, treatment with rhGH results in rapid acceleration in growth velocity and attainment of adult height within the normal range if treatment is initiated early. On average, children with GH deficiency gain approximately 30cm (12 inches) through rhGH therapy.^{12,19} In the other conditions for which rhGH therapy is FDA approved, lesser final height gains have been described. Using data from various studies it appears that height gains are approximately 3–9cm (1–4 inches) in chronic renal insufficiency, 5–8cm (2–3 inches) in Turner syndrome, 18–24cm (7–9 inches) in Prader–Willi syndrome, 13–16cm (5–6 inches) in SGA, 4–7cm (2–3 inches) in ISS, 8cm (3 inches) in SHOX deficiency, and 4–14cm (2–6 inches) in Noonan syndrome.^{20–28} These height gains suggest attainment of adult heights within the normal range for the majority of rhGH-treated children with chronic renal insufficiency, Prader–Willi syndrome, SGA, ISS, and Noonan syndrome, but not necessarily for most rhGH-treated children with Turner syndrome or SHOX deficiency.^{19–28}

Other Physical Effects

In GH-deficient children, rhGH treatment induces beneficial metabolic effects in addition to normalizing linear growth. Body fat is reduced, lipid profile and insulin sensitivity are improved, and bone mineral mass is increased.^{11,19,29} In children with Prader–Willi syndrome, many of whom have impaired GH secretion, improved body composition in response to rhGH therapy seems to be accompanied by functional improvements in strength, agility, and exercise tolerance, and motor skill acquisition in infants.^{30–32}

Psychosocial Effects

Many clinicians believe that short stature leads to psychosocial disadvantage,^{33,34} an idea that is supported indirectly by data suggesting that taller individuals or those who were taller during adolescence achieve higher income and occupational status, and that short children experience high rates of teasing and chronic psychosocial stress.^{35–37} Medically referred short children demonstrate lower social competence and more behavior problems compared with children of normal stature.³⁸ However, systematic analyses in the general population do not support a major impact of short stature on emotional wellbeing; specifically, short children and short adults do not seem to exhibit clinically significant psychosocial dysfunction.^{36,39–41} Moreover, GH treatment of children with short stature due to ISS and Turner syndrome has not been shown to substantially improve psychological adaptation or quality of life.^{38,42–45}

Safety

There is a long list of potential side effects with rhGH but each currently seems relatively rare. Adverse events include edema, benign intracranial

hypertension, slipped capital femoral epiphysis, scoliosis, growth of nevi, gynecomastia, pancreatitis, and features of acromegaly.^{12,19} In addition, there is some evidence that type 2 diabetes occurs with greater frequency in GH-treated patients; however, it appears to develop primarily in those already predisposed to the disease, and the overall incidence is low (34 cases per 100,000 years of rhGH treatment).⁴⁶ In overweight patients with Prader–Willi syndrome, rhGH therapy was associated with sudden respiratory death, possibly related to airway obstruction.^{47–50} Because of this association, sleep studies and airway assessments are recommended before initiating rhGH in patients with Prader–Willi syndrome.⁵⁰ Despite the apparently good safety record, the risks may be condition-specific (e.g. Prader–Willi syndrome), and there are substantial limitations to available evidence.⁵¹ Finally, there is a theoretical risk that treatment with rhGH, which is mitogenic, can facilitate neoplastic growth.^{52–54} Large epidemiologic surveys to date have not found an association between long-term rhGH use and malignancy in patients without risk factors for cancer.^{55,56} The importance of continued monitoring for possible associations between rhGH and cancer is highlighted by a long-term follow-up study showing that patients treated with twice or three-times-weekly cadaveric GH had higher incidences of colon cancer and Hodgkin's disease than the general population.⁵⁷ This finding is of uncertain relevance to patients treated with current rhGH dosing regimens and is difficult to interpret because cancer incidence in GH-deficient patients from the same period who were not treated with GH is unknown.⁵⁶

Ethical Considerations

The moral acceptability of GH therapy for short children without identifiable disease has remained controversial. Issues include whether treatment for marginally short children is appropriate, what degree of short stature constitutes a disability, how to distinguish between treatment of a potential disability and attempts at enhancement that are more cosmetic than medically driven, and the value of treatment.^{58–63} Expanded use of rhGH has also raised the important issue of distributive justice. Guaranteeing broad access to rhGH through public funds may result in diversion of limited healthcare resources from other necessary medical treatments. On the other hand, if private funds only are used to provide broad access to rhGH therapy, any benefit of therapy would be inequitably distributed to economically advantaged groups while any morbidity of short stature would be concentrated among those who are less wealthy.⁶³

Cost and Cost–Benefit Ratio

At \$40 per milligram, treatment with rhGH costs approximately \$20,000 per patient annually (as dose is weight-based, cost depends on the child's weight) and up to \$300,000 for a full multi-year course. This translates into a cost per inch gained in final height of \$24,000 (£6,000 per cm) in GH deficiency¹⁹ to \$35,000–\$50,000 in ISS.^{25,64} The cost of treating all US children with heights more than 2.25 standard deviations below the mean could exceed \$10 billion.¹³

A complete analysis of the costs of rhGH therapy in relation to its benefits is challenging, particularly because of the difficulty defining quality-of-life benefits derived from rhGH treatment and the potential differences in cost–benefit across disorders for which rhGH is used. Published cost–utility analyses of rhGH therapy for GH deficiency and

SGA performed by Novo Nordisk (a manufacturer of rhGH) concluded that the improved quality of life gained through rhGH therapy offset the financial costs,⁶⁵⁻⁶⁷ and systematic analyses not sponsored by industry are underway.

Other Burdens of Therapy

Subcutaneous injection of rhGH must be administered daily by a trained individual. Frequent follow-up with a pediatric endocrinologist and regular surveillance laboratory evaluations are also necessary.

Recombinant Human Insulin-Like Growth Factor-1 Height Attainment

In children with severe IGF-1 deficiency due to GH insensitivity or GH gene deletion with development of GH antibodies, rhIGF-1 can increase growth velocity from approximately 3cm/year pre-treatment to 8cm/year during the first year of therapy and 4–5cm/year thereafter.⁶⁸⁻⁷¹ Thus, growth velocity is markedly increased initially but then declines substantially. Final height has been obtained in five patients treated with rhIGF-1, and appears to be 10cm above predicted at baseline for patients with GH insensitivity.^{68,72} rhIGF-1 is not approved by the FDA for conditions other than severe primary IGF-1 deficiency or GH gene deletion with development of GH antibodies and the main US pediatric endocrinology professional group has recommended not using rhIGF-1 for other conditions at this time.¹⁵ However, a trial of two dosage regimens of rhIGF-1 in children with ISS and low IGF-1 level (more than two standard deviations below the mean for age) has been undertaken; first-year height velocity was 7–8cm/year in the rhIGF-1 treated group versus 5cm/year in the control group ($p < 0.001$ for each treatment group versus the control group). In the first year of treatment, skeletal age advanced more in the treatment groups at 1.1 and 1.2 years respectively compared with 0.8 years in the untreated group ($p < 0.002$ for each treatment group versus the untreated group).⁷³ There was no rhGH-treatment comparison group in that study, although it has been suggested that rhGH treatment of children with ISS may be expected to produce a more positive effect on adult height as it does not lead to advancement of osseous maturation compared with controls. The mean increments in growth velocities attained in this study (1.8cm/year and 2.7cm/year for the two treatment groups) have also been noted to be lower than the growth velocities achieved in patients with severe IGF-1 deficiency due to GH insensitivity treated with rhIGF-1 at the same doses (5.4 and 6.1cm/year, respectively).⁷⁴ Final heights for children with ISS treated with rhIGF-1 are not known.

Other Physical Effects

There are limited data on other physical effects of rhIGF-1 treatment. In a cohort of GH-insensitive patients, rhIGF-1 therapy was associated with a reduction in subcutaneous fat, increase in head circumference (suggesting brain growth), enhanced erythropoiesis, and elevated androgen levels in males.^{75,76}

Psychosocial Effects

The effect of rhIGF-1 treatment on psychosocial status is not known.

Safety

rhIGF-1 treatment of severe IGF-1 deficiency due to GH insensitivity or GH gene deletion with development of GH antibodies has been

associated with several mild to moderate adverse events. In the largest treatment study to date, hypoglycemia occurred in half (49%), injection-site hypertrophy in almost one-third (32%), and lymphoid hypertrophy in almost one-quarter (22%) of child subjects. Intracranial hypertension occurred in approximately 5%. Other adverse events reported in these patients include facial nerve palsy, parotid swelling, myalgias, headaches, and coarsening of facial features.⁶⁸ As children with GH insensitivity have an underlying predisposition to hypoglycemia, the increased risk due to rhIGF-1 treatment is unclear.

In patients with ISS treated with rhIGF-1, the most commonly reported adverse events were headache (36%), vomiting (24%), and hypoglycemia (15%).⁷³ Hypoglycemia associated with rhIGF-1 treatment in ISS is notable because it cannot readily be attributed to an underlying predisposition.⁷⁴ Other adverse events reported in the children with ISS treated with rhIGF-1 included lymphoid hypertrophy, intracranial hypertension, and myalgias.⁷³ As patients with certain malignancies have elevated levels of IGF-1 and IGF-1 can stimulate mitogenesis,^{53,54} there are additional as yet unproven concerns about rhIGF-1 treatment.

Ethical Concerns

As in rhGH treatment for ISS, potential expanded use of rhIGF-1 would raise issues of appropriateness, distributive justice and the ethical acceptability of pharmacologic therapy for short, otherwise healthy children. However, the issues are particularly problematic for rhIGF-1 because of the apparent relatively high risks associated with treatment, greater burden (twice daily injections), and availability of an effective alternative (rhGH) for such treatment.

Cost and Cost-Benefit

Annual cost of rhIGF-1 is approximately \$30,000 per child.¹³ If initiated early and continued until completion of growth, a full multi-year rhIGF-1 course could cost approximately \$300,000. While long-term treatment studies are scant, based on the estimated gain in adult height of 10cm (4 inches) in patients with severe primary IGF-1 deficiency, price per inch (2.54cm) of height gain may be roughly \$75,000. If use of rhIGF-1 expands to conditions such as ISS, for which another treatment (rhGH) is available, then cost-utility analysis should include comparison with rhGH.

Other Burdens of Therapy

rhIGF-1 treatment is relatively burdensome, consisting of twice-daily subcutaneous injections by a trained individual. Treatment surveillance also requires regular endocrinology clinic visits and laboratory monitoring.

Conclusion

Although many specialty drugs target life-threatening conditions, the two examples discussed here may be harbingers of the future in which advanced costly drugs are available for treatment of non-urgent, non-life-threatening conditions whose extreme forms may be disabling but whose milder forms affect primarily quality of life. The clear question will be how to best use such drugs—particularly in a system that puts increased emphasis on value and cost-effectiveness. This paper highlights the pros, cons, and unknowns regarding the use of two specialty drugs, rhGH and rhIGF-1, in the treatment of childhood short stature. Several features are noted. First, the adverse effects of rhIGF-1, its current

requirement for twice-daily injections, and its apparent (i.e. not yet tested in head-to-head comparisons) lesser final height prognosis compared with GH in ISS, give pause in considering expanded use of rhIGF-1 beyond FDA guidelines for defining clear GH insensitivity. Second, it is likely that the majority of children with ISS will not have clearly identifiable molecular or hormonal defects, and therefore decisions on their treatment may not ever rest on a specific diagnosis. When new molecular defects in GH and IGF-induced signal transduction are identified in individuals, they should not be construed as representing the likely situation for a majority of children with ISS unless there is clear evidence to that effect. The definition of ISS is largely a statistical one (i.e. height two standard deviations or more below the mean) and therefore even after all children with clear molecular defects are identified, there will still be children whose heights, by definition, will be two standard deviations or more below the mean. Third, to develop informed approaches to the use of the described specialty drugs in treating short stature, data are needed on their long-term outcomes regarding height, quality of life, psychological impact, and adverse events and comparisons of rhGH and rhIGF-1 (or combination) treatment in ISS. In addition, data are needed not only on criteria for beginning such expensive specialty drugs but also on when to stop them, since duration of treatment influences drug exposure and costs.^{34,77} Together, these data are needed to assess value-based use for such specialty drugs. Currently, if/when we treat children who have ISS with these drugs, we do so without the full benefit of important long-term data. Fourth, there is evidence that use of rhGH is strongly influenced by non-medical factors^{33,34,77} and the same may well be true for rhIGF-1. Accordingly, even full knowledge of efficacy using parameters described above may not alone clarify 'the right path' in using these medications. Family attitudes, physician attitudes, and demographics all currently influence use of the specialty drug rhGH; acknowledgement of, understanding of, and addressing these influences will be important in determining future use of specialty drugs for short stature. The difficulty is balancing the ability to 'do something' that appears to 'make a difference'

(i.e. increase growth) with perspective on our long-term goals for the individual child and for children as a whole: how much growth in relation to non-treatment has meaningful benefit (rather than simply having statistical significance), what height threshold is generally disabling (as opposed to simply less desirable), whether gains in height translate into improved quality of life (the underlying rationale for treatment), and some data-based perspective on risk-cost/benefit ratios. This delicate balance and judgment applies to many expensive specialty drugs and treatments but is particularly problematic for those that have debatable initiation criteria and unclear end-points, as often applies in treating short stature. While we may not be able to define the answers precisely, some approximation is necessary for policy-makers and patients as the healthcare system attempts to provide needed (but not necessarily discretionary) treatment in an informed, reasonable, and equitable manner. ■



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