Pharmacological Interventions for Short Stature: Pros and Cons

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Abstract
Although growth hormone (GH) therapy is virtually always effective in accelerating growth and restoring height potential to children with GH deficiency (GHD), the expansion of its use to a wide variety of other clinical disorders associated with short stature has resulted in considerable ethical and cost-benefit issues. Logic would demand that therapy should either be restricted to true ‘replacement’, thereby limiting its use to cases of unequivocal GHD, or treatment should be considered as a legitimate ‘enhancement’, and be available to all children with significant short stature. Consideration of the latter option requires a careful look at issues surrounding efficacy (both in terms of stature and any perceived disability resulting therefrom), cost and potential adverse effects. Similar concerns involve treatment with insulin-like growth factor-I and any related growth-augmenting therapy. To date, safety issues have been addressed through pharmaceutical-sponsored postmarketing surveillance studies. While of definite use, such investigations also have significant limitations, especially in addressing long-term concerns. The possibility of lifespan cohort studies, with surveillance of all GH recipients throughout life and comparison with data from appropriate controls, should be considered.

In 1926, the distinguished evolutionary biologist, J.B.S. Haldane, published a famous essay, ‘On Being the Right Size’, in which he wryly commented on some of the physical constraints that limit the size of organisms living on Earth: ‘For every type of animal there is a most convenient size, and a large change in size inevitably carries with it a change in form [1]’. As an example, Haldane imagined
a man 60 feet tall. Such an individual, if proportionate, would also be ten times as wide and ten times as thick as a normal-statured man, resulting in a 1,000-fold increase in mass. Every cross-sectional inch of leg bone would thus need to bear a 10-fold greater weight than normal human bone, and would, inevitably collapse (this is why the legs of elephants are so thick). Additional problems faced by such a tall individual include: (1) a need to pump blood to greater heights, requiring a larger heart, higher blood pressure, tougher blood vessels; (2) greater musculature to manipulate this 1,000-fold increase in mass; (3) an enormous increase in food and energy to support the required metabolism, and (4) a digestive system that could facilitate the necessary caloric requirements for such a great mass.

The principles of natural selection dictate that growth and form evolve so as to best promote the survival of the species and the transmission of its genome to the next generation. As Alfred Wallace wrote: ‘...necessary deduction from the theory of Natural selection, namely – that none of the definite facts of organic nature, no special organ, no characteristic form or marking, no peculiarities of instinct or of habit, no relations between species or between groups of species, can exist but which must now be, or once have been, useful to the individuals or races which possess them [2].’ In that context, it is of note that human growth velocity curves, at least as they relate to Homo sapiens, are characterized by several features which distinguish them from those of other species and which, presumably were ‘selected’ to maximize survival and reproductive capacity of our species: (1) maximal growth rate is during gestation; (2) birth is followed by a period of deceleration; (3) late sexual maturation (and epiphyseal fusion); (4) occurrence of puberty at the time of the slowest growth rate; (5) an adolescent growth spurt [3]. Of special note is the existence of an adolescent spurt in stature, essentially without parallel in other species, including primates, as well as a relative lack of sexual dimorphism in stature [4, 5]. Indeed, males and females are essentially of identical height prior to the onset of puberty, and the mean difference in adult stature of 12.6 cm between men and women can be virtually entirely ascribed to differential growth during puberty and the timing of epiphyseal fusion [6].

It is, thus, apparent that evolution, acting through natural selection, dictated patterns of fetal and postnatal growth that best suited H. sapiens as a species, including our need to accommodate and deliver a large fetal head, descend from an arboreal pattern of life, assume an upright posture for locomotion, and maintain arms and hands as free as locomotion would permit. When health and nutrition are not limiting factors, the growth patterns and adult heights achieved by humans are remarkably constrained, as evidenced by the relatively limited variation in adult stature for both males and females. It is against this background that pharmacological intervention to alter growth patterns and adult height must be considered.
The Growth Hormone Era

The only growth hormone (GH) that works in man is that derived from humans (or, potentially, other primates). The initial source of human GH (hGH) was from cadaver pituitary glands, requiring laborious and expensive collection of glands, followed by extraction and purification of hormone. The constrained supply limited its use to children with severe GHD, at restricted dosages and suboptimal schedules. With the approval of recombinant DNA-derived hGH, however, the potential emerged for essentially limitless supplies of hormone. Initial approval for treatment of children with GHD was followed, in short order, by approval for therapy for a large number of childhood conditions characterized by short stature, including Turner syndrome, renal failure, Prader-Willi syndrome, small for gestational age (SGA), SHOX deficiency, etc. (see table 1) [7].

The diagnosis of childhood GHD is often difficult, as GH is normally secreted by the pituitary in a pulsatile manner, with serum concentrations throughout the day often being quite low, interspersed with 6–8 spikes of secretory activity. The diagnosis of childhood GHD thus requires, in addition to characteristic growth patterns, demonstration that the patient fails to raise serum GH concentrations following pharmacological stimulation with a number of GH secretagogues. Such tests utilize nonphysiological stimuli and an arbitrary ‘cutoff’ level for peak serum GH, commonly set at 7 or 10 ng/ml. Given the frequent difficulty in establishing an absolute diagnosis, these criteria were constructed so as to avoid excluding a GHD child from receiving therapy, knowingly accepting the fact that treatment might be extended to some children without true GHD. Indeed, it is probable that the majority of children treated for GHD do not have any true GH secretory defect at all. While it is possible that GHD may represent a continuum of GH secretory defects, ranging from absolute to partial deficiency, establishing a diagnosis of GHD remains challenging, especially when the deficiency is not complete. In studies of responsiveness to GH therapy, children with peak provocative serum GH concentrations ≤2 ng/ml tend to grow better than children with higher peak GH levels, but the correlation

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<th>Table 1. FDA-approved uses of GH for promotion of height</th>
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<td>GHD of childhood</td>
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<td>Turner syndrome</td>
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<td>SHOX deficiency</td>
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<td>Prader-Willi syndrome</td>
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between peak GH levels and GH responsiveness is modest, at best, and virtually nonexistent with peak GH levels >2 ng/ml [8].

This issue was either resolved or rendered even more complicated by the approval by the FDA for GH treatment of ‘idiopathic short stature’ (ISS), defined as a height ≤−2.25 SD for age, with normal GH secretion and the absence of other known etiologies for growth failure. In essence, this approval resulted in rendering controversies concerning the diagnosis of GHD moot, since children who did not meet any set of arbitrary criteria for the diagnosis of GHD, could still potentially qualify for therapy under the diagnostic category of ISS. Indeed, in many cases, the deciding factor in the diagnostic categorization of a specific child was not identification of a specific etiology, but, rather, what diagnosis would be reimbursed by the patient’s insurance.

Ethical issues surrounding the use of GH for treatment of short children are, inevitably, complicated by: (1) the cost of treatment, which can range from USD 10,000 to 35,000 per year of treatment; (2) the variability in the growth response, due, at least in part, to the wide range of pathological conditions currently receiving treatment with GH; (3) the complex question of whether short stature, in and of itself, represents a disability, either in childhood or in adult life; and (4) potential adverse effects related to treatment. These are weighty questions and do not lend themselves to simple answers. At the very least, however, children currently receiving therapy for growth failure can be divided into three categories:

1. Children with unequivocal GHD, for whom GH treatment represents true ‘replacement’ therapy. In the overwhelming majority of such cases, if GH therapy is begun at an early age and administered at a proper dosage, the child can attain his genetic target height.

2. Children with underlying medical conditions, in which growth failure is a common feature, but not ascribable to defects of GH production. Such conditions include Turner syndrome, SHOX deficiency, chronic renal failure, and Prader-Willi syndrome (although some of the latter group may also have abnormal GH secretion). In such cases, GH therapy is not designed to replace a deficiency, but, rather, to override the underlying growth pathology by administering superphysiological levels of GH and, possibly, insulin-like growth factor-I (IGF-I). In general, such children show a partial response to GH therapy, accelerating growth, exceeding their otherwise destined adult stature, often achieving adult heights within the lower part of the normal range, but not attaining their full genetic target heights. To the conditions listed above, one might add a variety of chronic medical conditions frequently characterized by growth attenuation, such as inflammatory bowel disease, cystic fibrosis, chronic steroid use, etc., in which definitive data on improved growth are currently still unavailable.

3. Children in whom no underlying pathology, either endocrine or nonendocrine, can be demonstrated, but who are, nevertheless short. Some
of these children are simply constitutionally delayed and will, in time, have a late, but otherwise normal pubertal growth acceleration and attain normal adult stature without pharmacological intervention; these patients should not, in general, be considered suitable candidates for GH therapy. Other cases fall into the broad diagnostic category of ISS and, potentially, qualify for therapy with GH. A subset of ISS patients with severely low serum IGF-I concentrations despite normal GH secretion may be labeled as ‘severe primary IGF deficiency’ (IGFD) and qualify for treatment with IGF-I, although long-term data are still unavailable, except for patients with severe GH resistance [9]. Children born SGA and who fail to return to the normal range (i.e. >–2 SD) by age 2–4 years of age are also candidates for GH therapy.

In reviewing these categories, it becomes apparent that logic would dictate two potential approaches: (1) sharply limit GH treatment to children with unequivocal GHD, in whom treatment represents true replacement [the same may be true for IGF-I treatment of rare cases of severe GH resistance, resulting from mutations of the genes for the GH receptor (GHR), signal transducer and activator of transcription 5b (STAT5b), or IGF-I (IGF1)]; or (2) consider growth failure and short stature a ‘disability’, and make therapy available to all children meeting an arbitrary definition of short stature, regardless of the underlying etiology.

The ethical issues involved in choosing between these approaches have been well-summarized in a series of papers by David Allen and colleagues [10, 11]. An important factor lies in the definition of ‘disability’, and whether therapy represents ‘treatment’, or merely ‘enhancement’. Despite extensive anecdotal experience, as related by patients, parents and health care providers, there is little in the way of long-term controlled studies supporting the belief that such therapy provides clinically significant psychological or social benefit [12].

On the other hand, from the perspective of the small child, the etiology of the short stature is largely irrelevant. If the child perceives himself to be disadvantaged by his/her stature, it is of little importance whether GH treatment constitutes replacement of a deficiency or not. If, then, one argues that the etiology of the growth failure is not a critical issue, the key questions largely resolve into ones of efficacy, cost and safety.

Efficacy

As stated above, for the child with true GHD, GH therapy, if initiated at an early enough age, at a proper dosage and for a sufficient period of time before epiphyseal fusion occurs, can, typically, restore the child to his full genetic potential, in terms of stature. In the case of IGF-I treatment of severe primary IGFD, even in the most ‘classical’ cases, such as mutations of GHR, growth acceleration does
occur, but the degree of catch-up growth does not duplicate that observed with GH treatment of GHD, and few patients attain their full genetic target height. Nevertheless, the value of GH or IGF-I treatment, respectively, in unequivocal GHD or severe primary IGFD resulting from GHR defects, is unequivocal [7, 9].

For many of the other conditions currently treated, including FDA-approved indications, the long-term benefit is somewhat less certain. Data from multiple clinical trials in Turner syndrome and ISS indicate that GH therapy increases growth rate and adult height. For many patients, especially when treatment is initiated early in life at an adequate dosage, heights within the normal range for adult stature are attainable. On the other hand, larger dosages of GH are generally required than is true for GHD, the growth acceleration is more modest, and full attainment of genetic target height is often not possible.

Cost

The cost of GH or IGF-I is dosage-related, but, annual costs of USD 15,000–35,000 are fairly typical. In a child with GHD diagnosed at the age of 2 years, therapy would be continued until epiphyseal fusion, necessitating 10–15 years of treatment (not to mention the continued cost of lower dose GH therapy during adult life). For many of the other conditions commonly treated, relatively long-term treatment (usually at least 4+ years) is necessary to see the more modest improvement typically observed for these disorders. If one were to consider treatment for all children with heights <–2.25 SD (the current FDA-approved criterion for ISS) in the United States (~75,000,000 population <17 years of age), therapy would be required for ~900,000 patients. At an average annual cost of USD 20,000 per patient, this generates a total of USD 18 billion/year. Obviously, not all short children between birth and 17 years of age would be treated, and not for every one of their first 17 years of life, so this astronomical number requires serious adjustment. Nevertheless, an annual cost of USD 1.6–4 billion has been provided as a reasonable estimate of potential cost of treatment for short stature in the United States alone [10]. Whether such costs would be reimbursed by insurance is beyond the point, as this expenditure would have to come from somewhere in the healthcare budget.

Central to the issue of cost is the duration of treatment, which, at least in part, depends upon the ultimate goal of therapy, a matter for which no objective criteria have been identified. Should treatment continue until the child achieves a height within the broad 'normal range' (i.e. >–2 SD), or until he/she attains the mean stature for sex, or the parental genetic target height, or, perhaps, the height desired by the patient and family? And, of course, every time a short child is moved into the normal range, another child falls out of the normal range. It is, obviously, impossible for every individual to be between ±2 SD, just as it is impossible for every wage-earner to have an income above the national average.
Safety

The era of pituitary-derived GH ended in the early 1980s when it was shown to be associated with Creutzfeldt-Jakob disease, a devastating and lethal neurodegenerative disorder. rhGH has been in use now for over 25 years and has an enviable track record of safety. To date, most safety data derive from pharmaceutical company-sponsored postmarketing surveillance studies, which have reported findings in ~200,000 patients and >500,000 patient-years. Many of the GH-associated adverse effects have been related to rapid growth, such as progression of scoliosis or slipped capital femoral epiphyses. Others, such as increased intracranial pressure, are occasionally observed with a variety of hormone replacement therapies. Hyperglycemia and exacerbation of preexisting diabetes mellitus are rare, but not unanticipated consequences of GH treatment, given the known insulin antagonistic actions of GH. Recently, the long-term safety of rhGH was evaluated in almost 55,000 patients enrolled in the National Cooperative Growth Study, through the reporting of adverse events by prescribing physicians [13]. Nineteen of 174 deaths were considered by the physicians to be related to rhGH, although an additional 25 deaths were labeled as 'non-assessable' or had no reported causality. Although 2/3 of the assessable deaths were related to neoplasia, the authors concluded that the findings support a ‘favorable overall safety profile’.

It is necessary to point out that, despite the clear value of such postmarketing survey studies, they are characterized by a number of significant limitations: (1) reliance upon physician reporting of adverse events, as well as physician assessment as to whether such events are ‘GH related’; (2) incomplete enrollment of patients in such studies, with great variation in drug exposure and compliance with treatment regimens; (3) studies are time limited and are not necessarily designed for thorough follow-up of patients after treatment has ceased; (4) absence of any kind of suitable control group; (5) studies are under the supervision of the sponsoring pharmaceutical company, which control access, analysis and release of data, and (6) a lack of collaboration among the various postmarketing studies.

The issue of GH and/or IGF-related neoplasia has been a persistent concern, in light of substantial evidence supporting the involvement of the GH-IGF axis in the pathogenesis and progression of a variety of cancers [14–16]. Both GH and IGF receptors have been identified in cells from multiple forms of cancer, and both hormones have been shown, at least in cell culture and animal explant studies, to have potent mitogenic and proapoptotic actions. In a wide variety of animal models, manipulation of various genes involved in GH and IGF secretion and action have been shown to influence the occurrence or progression of cancers. Human epidemiological data are, at least to date, less convincing, although a recent report suggested that patients with GHR defects have a dramatic reduction in cancer frequency [17]. In a series of nested case-control
studies, a correlation has been reported between serum IGF-I concentrations in normal individuals and cancer risk. Although the conclusions of such studies are not always consistent, a recent meta-analysis of 26 investigations calculated the cancer risk at the upper quartile of serum IGF-I to be approximately 1.5 times that at the lowest quartile [18].

While studies of the risk of tumor recurrence in patients receiving GH therapy have been reassuring, some studies have suggested an increase in the frequency of second neoplasms in GH-treated cancer survivors [19]. Although these conclusions remain controversial, they serve to underscore the concern about a potential relationship between GH or IGF-I therapy and neoplasia, either primary or recurrent [20].

In late 2010, Agence Française de Sécurité Sanitaire des Produits de Santé issued a preliminary report concerning the findings of a long-term morbidity and mortality study [21, 22]. The French SAGhE (Santé Adulte GH Enfant) is part of a multinational European consortium, involving seven countries and entitled SAGhE (Safety and Appropriateness of GH Treatments in Europe); it is not clear why the French investigators elected to release the findings of their study separate from those of their collaborators [23]. In any case, the French investigation was based upon a mandatory registry of all patients treated with rhGH in France from the time of its introduction in the mid-1980s until 1997, encompassing approximately 7,000 patients carrying the diagnosis of idiopathic GHD, ISS or SGA, with a mean follow-up time of 16.9 years. For obvious reasons, an identical population of untreated children with these diagnoses was not available, and for comparison purposes, an age-specific French population was employed.

While the French report has yet to be published at this time, the results have been presented at a variety of national and international conferences. In the GH recipient group, 93 deaths were recorded, compared to an expected 70, yielding a standardized mortality rate (SMR) of 1.33. The total number of cancer deaths in the two groups was identical, although the investigators have emphasized an increase in bone-related cancer (3 cases vs. an anticipated 0.6). The greatest identifiable discrepancy between the two groups was in deaths related to ‘circulatory system’ disorders, where 9 were observed, compared to an anticipated 2.93, yielding an SMR of 3.07.

On the basis of these findings, the European Medicines Agency Committee for Medicinal Products for Human Use issued a statement of ‘no immediate danger’, but instructed prescribers to strictly follow approved indications and dosage. No critical evaluation of the findings was provided. Unfortunately, the French SAGhE study, which is to be commended for initiating and conducting an important investigation, is characterized by a number of significant weaknesses and limitations which should be identified and discussed in an open scientific atmosphere [24]. These limitations include, but are not limited to: (1) lack of a suitable control population; (2) failure to emphasize that conditions
such as idiopathic GHD, ISS and SGA may, in and of themselves, carry significant morbidities and may be characterized by unrecognized molecular and biochemical abnormalities; (3) failure to fully characterize a number of deaths labeled as ‘idiopathic’ or non-assessable, because no cause of death was recorded on the death certificate, and (4) questionable statistical evaluation of a number of the recorded morbidities and causes of death.

Conclusions

The use of agents such as GH and IGF-I as replacement treatment to accelerate growth and improve adult stature appears fully justified in conditions where therapy replaces an unequivocal deficiency, as is the case for GH treatment of GHD and IGF-I therapy for severe primary IGFD, where serum IGF-I cannot be raised through alternative means. Therapy with these agents in conditions where growth failure cannot be directly ascribed to a deficiency of the respective hormone is a more difficult issue, involving distinguishing between ‘treatment’ and ‘enhancement’, and weighing any perceived benefit against potential adverse effects and cost to the healthcare system.

As stated above, rhGH has had an excellent record of safety. Long-term experience with IGF-I is much less extensive, although no unexpected adverse events have been identified to date. It must be recognized, however, that even when therapy is directed at treatment of the cognate hormonal deficiency, the underlying disorder is not life threatening and that long-term adverse effects of treatment, even if only theoretical, must be considered. Postmarketing studies sponsored by the pharmaceutical industry, while of value, cannot be relied upon as the final arbiters of long-term safety. The SAGhE studies, including the French and other European investigations, represent an excellent effort to perform the necessary surveillance free of industrial oversight or interference, but have their own inherent limitations; furthermore, no similar studies have been undertaken within the United States.

In a recent publication in *The Journal of Clinical Endocrinology and Metabolism*, it was recommended that the endocrine community should endorse investigations of GH and IGF-I safety through establishment and follow-up of lifespan cohorts consisting of patients treated with GH or IGF-I during childhood, adolescence and adult life [24]. It was proposed that all GH/IGF-I recipients be included, regardless of underlying diagnosis. Such studies would be independent of commercial control, and instead be supervised by an independent, multidisciplinary investigative team with appropriate expertise and experience to assume primary oversight and conduct of a lifespan cohort.

This is, obviously, a highly ambitious undertaking, and pilot studies would be required to determine the feasibility of both retrospective and prospective enrollment, the appropriate mechanisms of follow-up, and the resources required for
initiation and maintenance of a lifespan cohort. Consideration must be given to issues such as sample size, statistical power, diagnostic categorization, sociodemographics, capacity to achieve comprehensive long-term surveillance, and the composition of the most appropriate control group(s). Despite these difficulties, lifespan cohorts have proven to be invaluable in assessment of risk/benefit of other treatment modalities, most notably chemotherapy in childhood cancer [25]. Without responsible data on long-term safety of growth-promoting agents, it is still impossible to provide any definitive assessment of the pros and cons of such therapy.

References


