

Ethical Issues in Growth Hormone Therapy: Where Are We Now?

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BACKGROUND

In 1991, a group of pediatric endocrinologists, ethicists, economists, and psychologists convened to address ethical questions arising from expanding use of recombinant human growth hormone (GH).¹ These included: (1) If GH was proven effective at improving the height of children without GH deficiency (GHD), is the diagnosis of GHD morally relevant in determining entitlement to GH treatment? (2) To what extent should the treatment of short stature (SS) be considered a medical problem requiring or justifying medical treatment? Much of the debate at that time centered around the argument put forth by Drs. Allen and Fost in a prior publication that GH responsiveness rather than GHD should guide access to GH.² Others at that conference countered that patients with GHD had a *disease* deserving *treatment*, while children with SS from other causes did not have a disease (at least not that of GHD) and to treat them is *enhancement* and not therapy.

The intervening years have not resolved this debate and new, equally important and problematic issues have arisen. The addition of Turner syndrome (TS) and chronic renal insufficiency (CRI) with SS to the list of approved indications for GH treatment validated the notion that GH effectiveness and not the underlying etiology of SS is the relevant variable in determining the appropriateness of treatment. With GH treatment no longer constrained by the treatment/enhancement distinction, numerous other SS conditions appeared as candidates. Further, new knowledge about important non-growth actions of GH and the importance of GH treatment of severe GHD in adulthood spawned interest in possible uses of GH in other types of SS in childhood. As GH utilization continues to expand, concerns and questions have been renewed about excessive expenditures of limited health-care resources. An additional question is, Can increased height measure the value of GH treatment and, if not, what can? To address these issues, 25 endocrinologists, ethicists, psychologists, and insurance representatives convened in October 1999 for a second ethics conference in Madison, Wisconsin. Adhering to the maxim that "good ethics begins with good facts," an initial session focused on current knowledge regarding the benefits and burdens of GH treatment in children with GHD, TS, and Prader-Willi syndrome (PWS), and in adults with GHD. A second session analyzed how decisions guiding access to GH treatment are and should be made from the perspectives

of local insurance providers, planners of the Oregon Health Plan, and individuals considering the national health-care economy. The group then debated the proper endpoint of GH treatment in children: Should it be the maximal attainable height or simply "normal" height, or should psychosocial adaptation, rather than height, be the appropriate endpoint? Finally, conceptual issues raised by the initial conference¹ were revisited: Specifically, is the treatment/enhancement distinction helpful in guiding access to GH treatment, and how should the use of GH treatment be determined in the context of the American health-care system?

SCIENTIFIC ISSUES

Dr. Margaret MacGillivray, a pediatric endocrinologist, presented current data describing adult heights of hypopituitary children treated recently with GH (– 1.5 to – 0.7 SDS). The result is a marked improvement in final height compared with former treatment with pituitary-derived GH (– 4.7 to – 2.0 SDS). She predicted further improvements with earlier treatment and improved pubertal GH replacement.

Dr. David Sandberg, a psychologist, then addressed perhaps the most complex and contentious topic of the conference: What do we know about the quality-of-life (QOL) benefits of GH-increased final height? While acknowledging the daunting methodologic challenges of such research, he reported that his and other studies failed to show a relationship between adult height and QOL, suggesting that maximizing adult height outcomes does not automatically translate into improved QOL outcomes. Such observations, if confirmed, will have clear relevance to questions regarding both termination of GH therapy and GH treatment of non-GHD children for presumed psychosocial benefit.

The successful treatment of TS girls with GH is now regarded as standard practice, but is the benefit of treating these children truly clinically significant? Dr. Ron Rosenfeld, a pediatric endocrinologist, was assigned the "pro" position for this debate. He presented evidence that GH accelerates growth and improves final height in TS, that this outcome can be achieved without excessive delay in pubertal development, and that GH is safe for these patients. Anecdotal experience suggested a beneficial effect of GH therapy on QOL in children and young adults with TS, but studies assessing impact of growth-promoting therapy on psychosocial function are lacking. Conclusive data will be extremely difficult, if not impossible, to obtain in the current environment. Dr. Harvey Guyda, also a pediatric endocrinologist, was assigned the "con" position. He argued that the desired outcome for most patients (achiev-

ing a “normal” height) does not occur for the majority of TS girls treated with GH. The median final height achieved by patients in the Canadian randomized controlled study is only – 2.3 SDS. While some individuals have shown dramatic responses, only ~50% of those in the Canadian study can expect a height benefit >5 cm. Further, Guyda emphasized that treatment has not been proven to lead to improved psychosocial functioning. A challenge remains to determine methods to identify the TS patients who are most likely to benefit from prolonged GH treatment.

The determination of a responsible endpoint for GH therapy for growth promotion in all conditions remains problematic. Dr. David Allen, a pediatric endocrinologist, proposed that treatment should be stopped when the height is within the normal adult range. This represents not only a successful therapeutic outcome but also a more reasonable allocation of resources and preservation of a proper goal for the medical profession in the treatment of SS. On the other hand, Allen stated, since many children with unexplained isolated GHD display normal GH secretion after puberty, continuous treatment to maximal height may include years of unnecessary treatment, during which time GH therapy becomes increasingly expensive and, simultaneously, less effective as final height is approached. From an ethical standpoint, Allen stated, promoting additional growth within the normal adult range could be viewed as enhancement and not treatment. Dr. Michael Kappy, a pediatric endocrinologist, countered that using the lower range of adult height as a goal represented a gender-biased definition of handicap, since demands for daily living (eg, reaching for objects on a high shelf) are not gender-specific functions. Instead, the criterion for discontinuing GH should be purely physiologic, ie, how tall the child would have grown if he or she did not have GHD. He argued that this approach was less arbitrary and reduced the risk that the physician would need to make value judgments.

Novel uses of GH treatment add complexity in identifying appropriate recipients and in determining appropriate outcomes for judging the value of such treatment. For example, adults with severe GHD have abnormal body composition, deficient bone mineral density (BMD), lipid abnormalities, and a decrease in QOL. Dr. David Cook, an internist and endocrinologist, emphasized that while several such entities appear amenable to GH replacement therapy, the focus of insurance companies is favorable changes in mortality figures and reduced bone fracture rates, rather than QOL or metabolic issues. However, awareness of these non-growth or metabolic effects of GH has raised interest in the effect of GH therapy on body composition and physical function in disabled children, such as those with PWS. Dr. Aaron Carrel, a pediatric endocrinologist, reviewed data showing that in PWS children GH therapy improves body composition such as reducing body fat and increasing lean body mass, BMD, fat oxidation, and energy expenditure. Most importantly, physical strength and agility are improved. These benefi-

cial effects were viewed by families to be as important or even more important to the well-being of the child than gain in height. The view of many insurance companies may not be in accord with the views of physicians who are treating these children.

ETHICAL, SOCIAL, ECONOMIC, AND POLICY ISSUES

Appropriately, the conference then turned its attention to ethical, social, economic, and policy issues regarding access to GH therapy. The medical directors of 3 Wisconsin-based HMOs presented their organizations’ policies on paying for GH treatment and explanations of how such decisions are made. While all 3 HMOs seemed to use similar approaches, their conclusions were disturbingly divergent. One provided full reimbursement for treatment for GHD and TS; one required 50% copayment; and the third paid nothing for either indication. They all claimed to rely on medical necessity as the central criterion for resolving such questions, but the definition of this term was unclear.

Mark Pauly presented an economist’s perspective, one based on the assumptions that GH was safe, effective, and available in unlimited supply, and that market conditions were ideal, including that potential purchasers had full knowledge of the facts. In such a system, the most generous insurance packages would probably cover treatment for very short children with GHD, but that this would be less likely for children already in the normal range or for conditions for which treatment produced only minimal increases in height. He thought it likely that there would be public support to subsidize only the most severely affected children.

With regard to accepting private purchase of GH for children who were not severely affected, this appeared compatible with existing notions in the United States of tolerating individual discretion in spending earned income for health matters, particularly if these decisions did not cause severe harm to those who could not afford treatment. Given the apparently modest gains produced by GH treatment in most non-GHD children, Pauly thought it unlikely that there would be severe overall harm. To him the inequality likely to be produced by such private purchases seemed trivial compared with other consequences of inequality of wealth that are currently prevalent.

Philosopher Paul Menzel described the approach of the Oregon Health Plan with regard to access to GH by its Medicaid population. Oregon has identified 743 “treatment/condition pairs,” and currently prioritizes funding down to No. 574. Pituitary dwarfism is included (No. 499), as is GH therapy for TS (No. 506). GH treatment is not supported for any other conditions that presumably fall into the generic category, listed at No. 736, which is titled, “Endocrine or metabolic conditions with no effective treatment or where no treatment is necessary.” (However,

which criterion was considered relevant in the exclusion is unclear.) Menzel suggested that from the perspective of social justice in access to health care, the apparently marginal benefit of GH treatment of most non-GHD children with regard to the modest increase in height should not cause great alarm. To the contrary, the more important question might be whether the benefits that accrue to patients with TS can be justified in the Oregon plan when one considers other possible use of the funds.

Pediatrician Douglas Diekema questioned the claim that treatment with GH is a net benefit, particularly for children without GHD. He focused on the ambiguity of psychosocial benefit and thought more consideration should be given to the potential psychological harm of treatment, which is supported by some studies. This could occur from an implied message to children that their parents are unaccepting of them. This may be particularly problematic when treatment produces little or no increase in height. He also pointed out that treatment of these children does not make them tall but only less short.

Dr. Norman Fost, a pediatrician and ethicist, reviewed the hazards of trying to resolve questions of access by relying on traditional distinctions made between health and disease and between treatment and enhancement. He argued that some conditions are clearly diseases, such as the persistent vegetative state, and yet might not warrant expensive prolonged treatment. Similarly, some conditions are clearly not diseases, such as pregnancy, and yet attract wide support for treatment to be included in a basic benefits package. He applied similar analyses to treatment versus enhancement distinctions, stating that some clear treatments did not warrant funding and some clear enhancements did. The latter could include bringing "normal" short children into the normal height range.

Philosopher Allen Buchanan discussed GH as a paradigm of "expansive biotechnologies," which refers to technologies that begin as clear medical treatments and then are found to offer benefits that do not clearly belong in the health-care system. Few would dispute that pituitary dwarfism is a medical problem warranting medical treatment, but many of the newer applications of GH, such as producing marginal increments in height or improving strength or slowing the aging process, are not so clearly defined as medical problems. He compared GH with other technologies and drugs, including artificial insemination and Prozac. These began as treatments for medical problems but expanded to much larger markets that involved problems that were less clearly medical. He expressed concern that these expanding uses for very expensive technologies "might erode our society's already shaky commitment to the right of an adequate level of health care for all."

Philosopher Dan Brock concluded the conference with several summary observations. He cited the need for a clear formulation of the ultimate endpoints we seek from

GH treatment. He also cited the lack of data on the degree to which current endpoints are achieved. He stated that height itself cannot be an appropriate endpoint because "it is only instrumental to improvements in patients' quality of life." He urged that future studies focus on QOL gains since coverage by insurance would be difficult to justify without clearly established QOL benefits. He concurred with Dr. Fost that whether SS is a disease, and whether use of GH is characterized as treatment or enhancement, would not resolve the critical questions.

In reviewing Dr. Pauly's presentation, he noted that health-care markets do not function well, and the inequities in income distribution may be difficult to justify, so that leaving access to the market would be difficult to support as a matter of social justice. On the other hand, Dr. Pauly acknowledged the practical and theoretical difficulties in limiting the freedom of those with discretionary money to spend it as they wish. Brock reminded the group of the axiom that one cannot go from an "is" to an "ought," so that the present arrangements in income distribution and health care cannot be presumed to be fair. He acknowledged that we do not yet have an adequate framework for resolving problems of access and rationing.

CONCLUSION

A decade ago, Allen and Fost asked whether GH therapy would become a panacea or Pandora's box. The question remains unanswered. Viewpoints expressed at this conference suggest that while some issues have been clarified, new questions have arisen. While GH can increase final adult height in some patients, the effect on their QOL remains unclear. While the safety of long-term GH therapy is clearer, the costs continue to be high, and new indications, such as treatment for metabolic reasons, and new questions about who should have access to GH and who should pay remain unanswered. The other questions asked by Drs. Allen and Fost in 1991 also remain unanswered. Continued frequent discussion of these issues by physicians, ethicists, health economists, and others together is essential if responsible and equitable use of GH during the next decade is to occur.

REFERENCES

1. Allen DB, Fost NC. Access to treatment with human growth hormone: proceedings of a conference. *GROWTH, Genetics, & Hormones* 1992; 8 (supplement).
2. Allen DB, Fost NC. Growth hormone therapy for short stature: panacea or Pandora's box? *J Pediatr* 1990;117:16-21.

PUBLICATION NOTE

The complete proceedings of the conference, including presented papers and an edited transcript of the discussions, will be published as a supplement to *Pediatrics*.
