Long-Term Surveillance of Growth Hormone Therapy

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Human cadaveric GH (hGH) first became available for treatment of GH deficiency (GHD) in the early 1960s. Distribution was terminated in the 1980s when it was discovered to be associated with Creutzeldt-Jakob disease, but recombinant hGH (rhGH) quickly took its place and now has been in use for over 25 yr. Access to essentially unlimited supplies of rhGH facilitated expansion of Food and Drug Administration (FDA)-approved indications for therapy, which now include childhood and adult GHD, Turner syndrome, chronic renal failure, small for gestational age (SGA), Prader-Willi syndrome, Noonan syndrome, SHOX deficiency, idiopathic short stature (ISS), short bowel, and AIDS wasting.

rhGH has an enviable track record of safety. Enrollment in pharmaceutical company-sponsored postmarketing surveillance studies involves approximately 200,000 patients and more than 500,000 patient-years. Although a great deal of valuable information has been accumulated, these studies have methodological limitations, are open-label, and are not supervised by any external, independent, data-monitoring group. In a recent report from the National Cooperative Growth Study, "long-term safety" of rhGH was evaluated in 54,996 patients by means of adverse event reports submitted by prescribing physicians (1). Nineteen of 174 deaths were considered to be related to rhGH, but an additional 25 were either "not assessable" or had no reported causality. Two thirds of the assessable deaths were related to neoplasms, with the other deaths attributed to a variety of causes. The authors concluded that these findings support a "favorable overall safety profile," but cautioned that specific populations might be at risk for adverse effects.

In December, 2010, Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) released a preliminary report of the findings of a long-term morbidity study, Sante Adulte GH Enfant (SAGhE), based upon a mandatory registry of all patients treated with rhGH in childhood in France from its introduction in the mid-1980s until 1997 (http://saghe.aphp.fr/site/spip.php/). The defined population of approximately 7000 children included patients carrying diagnoses of idiopathic GHD and ISS and short stature children born SGA. The mean follow-up time from treatment initiation to last contact or death was 16.9 yr. Because an identical population of untreated children with short stature was not available, comparison of mortality was performed using age-specific French population-based mortality rates.

The announcements from AFSSAPS and the European Medicines Agency (EMA) provide a summary of the key findings, which have also recently been presented at the 93rd Annual Meeting of The Endocrine Society (2) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001160.jsp&murlmenus/news_and_events/news_and_events.jsp&midWC0b01ac058004d5c1)

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Abbreviations: GHD, GH deficiency; hGH, human GH; ISS, idiopathic short stature; rhGH, recombinant hGH; SGA, small for gestational age.

but are not yet published in a peer-reviewed journal. The French study is part of a European consortium entitled SAGhE (Safety and Appropriateness of GH Treatments in Europe) involving seven additional countries; the findings from this much larger cohort (estimated size 20,000–30,000) will become available in future years.

Data from the French SAGhE study, using age-specific mortality rates, indicate that there had been 93 deaths in the rhGH cohort, compared to an expected 70 deaths, yielding a standardized mortality ratio of 1.33. The majority of this difference in total deaths was in the category "idiopathic," meaning that no cause of death was stated on the death certificate or that investigators were unable to determine the cause of death (21 "idiopathic" deaths in the GH-treated group *vs.* seven expected). The total number of cancer-related deaths in the two groups was identical, although there were three cases of incompletely defined "bone cancer" in the treated group, compared with an anticipated 0.6. The greatest identifiable discrepancy was "circulatory system" deaths, which numbered nine in the treated group, compared with an anticipated 2.93 (standardized mortality ratio = 3.07), although these deaths were related to heterogeneous conditions, such as cardiomyopathy and subarachnoid or cerebrovascular hemorrhages.

The report also described an increased risk in patients receiving GH dosages above 50 μg/kg · d, although the case numbers at high GH dosages were relatively small (<300) and were heavily weighted toward children categorized as SGA.

On the basis of these findings, the EMA's Committee for Medicinal Products for Human Use (CHMP) promised to review all available data to assess risk-benefit balance. CHMP confirmed that there was "no immediate danger" but instructed prescribers in Europe to strictly follow approved indications and dosages. In August, 2011, the FDA, on the other hand, after reviewing the French SAGhE study, determined that "at this time, the evidence regarding recombinant hGH and increased risk of death is inconclusive," and identified a number of study design weaknesses that limit the interpretation of study results.

Although the French report has yet to be published, it has already generated questions, concerns, and controversy. The release of incomplete information from the SAGhE report by various agencies, before proper peer-review had occurred, poses great difficulties in analyzing the results and recommendations. Importantly, given that children with the diagnoses of GHD, ISS, and SGA may be at risk for specific morbidities, even in the absence of therapy, the lack of an untreated control group in SAGhE is especially problematic. Although many of the questions emanating from SAGhE, particularly in reference to cancer risk, have been raised in the past, they continue to generate concern (3, 4). Accordingly, this would seem to be an appropriate time to place such questions in perspective and to suggest a means for addressing them as comprehensively as possible.

Theoretical, Epidemiological, and Clinical Bases for Concerns about Cancer and Mortality in GH Recipients

Substantial evidence exists supporting the involvement of the GH-IGF system in the pathogenesis and progression of various cancers (3–5). IGF and GH receptors are found in multiple tumors, and these hormones have potent mitogenic and antiapoptotic activities in both normal and malignant cells. Over a dozen genes in pathways regulating GH and IGF secretion and action have been genetically manipulated in animal models. In general, when GH/IGF secretion or action is inhibited, a decreased incidence and rate of progression of cancers have been observed.

Human populations with specific mutations in the GH-IGF system have been characterized for cancer risk. Recent reports have suggested that individuals with GH receptor deficiency may have a dramatic reduction in cancer frequency (6). Data from nested case-control studies indicate a correlation between cancer risk and circulating levels of IGF-I; a recent meta-analysis of 26 studies calculated the risk at the upper quartile of serum IGF-I to be approximately 1.5 times that at the lowest quartile (7). Given these concerns, an emerging practice among pediatric and adult endocrinologists involves titrating GH dosage to achieve serum IGF-I concentrations that are perceived as both efficacious and safe (8).

IGF-I Therapy

IGF-I is approved therapy for patients with severe primary IGF-I deficiency, although long-term experience is still limited. Many of the theoretical concerns involving GH also relate to IGF-I treatment. To complicate matters further, preliminary results of clinical trials with combination GH + IGF-I have demonstrated excellent short-term growth, but at the price of serum IGF-I concentrations well above the normal range. The long-term risks of such high serum IGF levels remain to be determined.

GH Therapy in Cancer Survivors

To address concerns regarding the potential for GH therapy to increase the risk of tumor recurrence or promote the

development of new neoplasms in survivors of childhood cancer, the Childhood Cancer Survivor Study (CCSS) investigated 13,500 five-year survivors (9). Among the 361 GH-treated survivors, no increased risk of disease recurrence was found with adjustment for demographic and cancer treatment factors.

Initial assessment of second and subsequent malignancies in survivors of childhood cancer in the CCSS cohort found the relative risk of a second neoplasm among GH-treated survivors to be 3.21 (10). In an updated analysis with an additional 32 months of follow-up, a total of 20 neoplasms had occurred in 361 GH-treated cancer survivors, providing a relative risk of 2.15 (95% confidence interval, 1.3–3.5; $P = 0.002$) (11), although these conclusions remain somewhat controversial (12, 13).

Long-Term Surveillance of GH-Treated Patients

With the exception of the studies involving cancer survivors, investigations of GH safety have been largely limited to postmarketing surveillance sponsored by several pharmaceutical companies. Although generally reassuring, these investigations have a number of important limitations: 1) reliance upon physician reporting of adverse events, and physician evaluation of whether such events are "GH-related"; 2) they are time-limited; a number of the major studies have stopped recruiting patients or halted collection of additional data; 3) absence of a control group of any kind; 4) each study is under the control of its sponsoring company, with no attempt to coordinate data analyses; and 5) all data are under the jurisdiction of the sponsoring company, which dictates the nature of any analyses that are performed.

The SAGhE studies represent the first effort at longer-term investigations in children receiving GH and, additionally, are independent from commercial oversight. These investigations are limited, however, by the lack of an ideal control group of untreated patients (perhaps an unavoidable situation), by modest patient numbers and by inherent difficulties in the integration of data and protocols from different countries. No similar studies have been undertaken in the United States. Because GH and IGF-I recipients are, by and large, otherwise healthy individuals, and because therapy is often given for years, if not decades, the concerns discussed above mandate more rigorous and longer-term evaluation.

To comprehensively evaluate the long-term health consequences of GH treatment, it will be necessary to have an appropriately designed cohort(s) characterized by: 1) adequate sample size and statistical power; 2) individuals who are well-characterized relative to underlying disorder (including etiology, severity, genetic syndromes, comorbidities, and response to treatment), as well as sociodemographics; 3) accurate documentation of GH treatment and response; 4) capacity to achieve comprehensive long-term surveillance, including documentation of adverse outcomes; and 5) an appropriate control group or the ability to perform meaningful comparisons of observed outcomes to expected outcomes (14).

There are a number of formidable challenges with regard to designing trials that will have sufficient statistical power to rule out designated levels of risk in GH recipients. Issues such as the low incidence of potential adverse events, the need to consider potential confounding factors, and the required duration of follow-up make it clear that rigorous assessment of long-term safety will demand a cohort(s) of substantial size.

Characterization of exposure to GH or IGF-I should be as detailed as possible relative to dose and duration, to determine whether there exists a dose-response relationship, which may provide greater biological plausibility for any observed association. Capturing detailed treatment information can be difficult and labor intensive. Thus, careful consideration should be given to the extent of exposure assessment that is undertaken, while recognizing that deficiencies in length of follow-up may undermine the integrity of the overall study design.

Essential to the design of a cohort study to evaluate the long-term safety of GH or IGF-I treatment is the ability to successfully carry out extended surveillance (either retrospectively or prospectively) of the eligible population. It may be necessary to rely on direct reporting from the individuals and/or healthcare providers, with subsequent validation through medical records.

Critical to cohort design is the proposed comparison population, ideally consisting of nontreated individuals carrying the same diagnoses and matched for sociodemographic characteristics. Identification of such untreated control populations is difficult for GH therapy, but every effort should be made to accrue data on patients with GHD, ISS, Turner syndrome, or SGA who have not received GH. Although cancer- and mortality-related statistics are usually available for the general population, calculation of expected number of other outcomes, such as cardiovascular events, may be difficult.

Summary and Recommendations

Establishment of carefully considered cohort(s) must be a priority, if one accepts that long-term safety of GH and IGF-I treatment constitutes an obligation of the

healthcare community, pharmaceutical industry, and regulatory agencies. Regardless of study design, this will require substantial commitments of both resources and expertise. This being said, we put forward the following recommendations:

1. The endocrine community should endorse investigation 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. Inherent in this endorsement is a commitment to facilitate identification and subsequent enrollment of all eligible patients. All GH recipients should be included, regardless of underlying diagnosis.
2. The pharmaceutical industry, National Institutes of Health, FDA, and EMA should not only endorse establishment of lifespan cohorts, but also commit adequate financial support for the design and conduct of long-term follow-up into late adulthood.
3. A multidisciplinary working group of independent researchers should be established and charged with the design of a cohort study to rigorously investigate health outcomes across the lifespan of patients treated with GH or IGF-I during childhood, adolescence, and adult life. This group must be independent of commercial oversight.
4. Pilot studies should be designed and conducted to determine: 1) feasibility of retrospective/prospective enrollment; 2) mechanisms of follow-up; and 3) resource requirements for a lifespan cohort.
5. An independent investigative team with the appropriate expertise and experience to assume primary oversight and conduct of the lifespan cohort should be selected.
6. An international workshop should be convened and designed to summarize ongoing and proposed efforts to: 1) understand the molecular and physiological bases for GH- and IGF-related adverse events; and 2) evaluate long-term safety of GH and IGF-I therapy, with the objective of coordinating efforts to comprehensively and efficiently assess long-term safety.

rhGH therapy has had a long and distinguished track record of both efficacy and safety. Although experience with IGF-I is much more limited, it is a highly promising treatment for many children incapable of responding appropriately to GH. We must, nevertheless, remain cognizant that any therapy carries risks of long-term morbidities and that it is the responsibility of the medical community to provide appropriate surveillance. Although we have every expectation that the measures proposed herein will evoke controversy, we believe that such discussions are important. The active involvement of major societies, such as (but not necessarily limited to) The Endocrine Society, the Pediatric Endocrine Society (PES/LWPES), the European Society for Pediatric Endocrinology (ESPE), the GH Research and IGF Societies, and the American Association of Clinical Endocrinologists, in evaluating steps for proper monitoring of long-term GH and IGF safety is clearly both necessary and welcome at this time.

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References

1. **Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B** 2010 Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 95:167–177
2. **Carel J-C, Ecosse E, Landier F, Meguellat-Hakkas D, Kaguelidou F, Rey G, Coste J** Long-term mortality after recombinant growth hormone treatment for isolated childhood short stature: report of the French SAGhE study. Program of the 93rd Annual Meeting of The Endocrine Society, Boston, MA, 2011 (Abstract LB-5)
3. **Swerdlow AJ, Higgins CD, Adlard P, Preece MA** 2002 Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. Lancet 360:273–277
4. **Cohen P, Clemmons DR, Rosenfeld RG** 2000 Does the GH-IGF axis play a role in cancer pathogenesis? Growth Horm IGF Res 10:297–305
5. **Chhabra Y, Waters MJ, Brooks AJ** 2011 Role of the growth hormone-IGF-1 axis in cancer. Expert Rev Endocrinol Metab 6:71–84
6. **Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P, Longo VD** 2011 Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci Transl Med 3:70ra13

7. **Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M** 2004 Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 363:1346–1353
8. **Cohen P, Germak J, Rogol AD, Weng W, Kappelgaard AM, Rosenfeld RG; on behalf of the American Norditropin Study Group** 2010 Variable degree of growth hormone (GH) and insulin-like growth factor (IGF) sensitivity in children with idiopathic short stature compared with GH-deficient patients: evidence from an IGF-based dosing study of short children. J Clin Endocrinol Metab 95:2089–2098
9. **Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, Green DM, Hammond S, Meadows AT, Mertens AC, Mulvihill JJ, Nathan PC, Neglia JP, Packer RJ, Rajaraman P, Sklar CA, Stovall M, Strong LC, Yasui Y, Zeltzer LK** 2009 The Childhood Cancer Survivor Study: a National Cancer Institute-sponsored resource for outcome and intervention research. J Clin Oncol 27: 2308–2318
10. **Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, Yasui Y, Robison LL** 2002 Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 87:3136–3141
11. **Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W, Yasui Y, Robison LL, Sklar CA** 2006 Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor study. J Clin Endocrinol Metab 91:3494–3498
12. **Mackenzie S, Craven T, Gattamaneni HR, Swindell R, Shalet SM, Brabant G** 2011 Long-term safety of growth hormone replacement after CNS irradiation. J Clin Endocrinol Metab 96:2756–2761
13. **Wilton P, Mattsson AF, Darendeliler F** 2010 Growth hormone replacement treatment in children is not associated with an increase in the incidence of cancer: experience from KIGS (Pfizer International Growth Database). J Pediatr 157:265–270
14. **Colditz GA** 2010 Ensuring long-term sustainability of existing cohorts remains the highest priority to inform cancer prevention and control. Cancer Causes Control 21:649–656