Critical Evaluation of the Safety of Recombinant Human Growth Hormone Administration: Statement from the Growth Hormone Research Society*

This document reflects what has been learned about the safety of recombinant human GH since its introduction to the market in 1985. These lessons are the result of an unprecedented level of scrutiny that has lasted more than 15 yr and continues today. The Creutzfeldt-Jakob disease epidemic due to contamination of pituitary-derived GH, the Japanese reports on a potential association between GH and leukemia, and the fact that GH was the second recombinant product brought onto the market were important considerations behind the need for such careful surveillance.

GH, insulin-like growth factor (IGF)-I, and cancer risk based on epidemiological and experimental data

Epidemiological data. Active acromegaly, a disease characterized by raised serum GH, IGF-I, and IGF-binding protein (IGFBP)-3 levels, has been reported to be associated with an increased incidence of colonic neoplasia, although conflicting data do exist. There are no convincing reports of an increased incidence of breast or prostate cancers in this condition.

Recent epidemiological studies, including case-control as well as prospective designs, report that serum IGF-I levels in the upper normal range may be associated with an increased risk of developing prostate cancer and breast cancer in premenopausal but not postmenopausal women. In addition, the combination of high IGF-I and low IGFBP-3 levels in serum may be associated with an increased risk of these two tumors as well as the risk of colon cancer. High serum IGFBP-3 levels alone have also been related to a reduced cancer risk. Importantly, however, a cause-effect relationship between cancer risk and either IGF-I or IGFBP-3 has not been demonstrated. Serum IGF-I levels may be determined by additional factors other than GH status, including nutrition.

Experimental studies in vitro and in animal models. Most cells, including cancer cells, possess IGF-I receptors and respond to IGF-I with increased growth. IGFBPs and IGFBP proteases also modulate cell growth, and overexpression of IGF-I receptors induces tumor formation in animal models. Nevertheless, there is no evidence that systemic administration of IGF-I to animals stimulates tumor formation, although it can increase growth of some established tumors. No studies have evaluated the direct (IGF-independent) effects of GH on tumor formation. In GH transgenic animals specific activation of GH receptors with concomitant elevations in circulating IGF-I did not result in breast, colon, or prostate tumor formation.[1]

GH replacement and cancer risk. There are no data to suggest that IGF-I and IGFBP-3 modulate cancer risk in GH-treated

patients. Patients with previous malignancies or a history of radiation therapy carry a significant risk for recurrence and second malignancy. However, as part of management, we recommend measurement of serum IGF-I levels in patients receiving GH treatment. The place of regular IGFBP-3 monitoring is not defined. In GH-deficient adults, it is recommended that the IGF-I level is maintained within the appropriate age- and gender-related normal range during long-term therapy.

Regulatory aspects. The current labeling for GH states that active malignancy is a contraindication for GH treatment. There are, however, no data to support this labeling. Current knowledge does not warrant additional warning about cancer risk in the product label.

Safety aspects of GH therapy in children

Recombinant human GH has been used in an estimated number of close to 100,000 children. Significant adverse drug reactions are rare. The large international databases have been useful in quantifying adverse events and, hence, addressing safety issues. Extended monitoring into adulthood of children who have discontinued GH treatment would be ideal but may only be achievable in a subset of patients. The principal safety issues in children relate to the following areas:

Malignancy risk. Children receiving GH, who have had a malignancy, account for approximately 20% of patients enrolled in international databases. Existing evidence does not indicate that GH treatment will increase tumor recurrence in those successfully treated for their primary lesion. In these patients, who have been rendered GH deficient by the tumor and/or its treatment, the timing of initiation of GH treatment must be decided on the basis of the individual case, once tumor treatment is completed and the condition is in remission.

All subjects who have had a malignancy and received treatment for it are at risk for a second malignancy. There is no evidence that GH treatment increases the risk of this process based on the limited data available. Neither is there evidence that *de novo* cancer and leukemia are increased in GH recipients. In view of the continuing evolution of oncology treatments, ongoing surveillance of GH recipients with appropriate age-related controls is important.

Certain patient groups, who occasionally receive GH treatment, carry an intrinsic risk of developing malignancies including those with neurofibromatosis type 1, Down's and Bloom's syndromes, and Fanconi's anemia. Although there is no evidence that GH replacement poses an increased cancer risk, we recommend that such children will be carefully monitored with regard to tumor formation.

Benign intracranial hypertension. Benign intracranial hypertension is reported in 1/1000 children receiving GH treatment. This may be an underestimate. Therefore, headache in children on GH treatment should be carefully evaluated. Fundoscopic examination should be performed before the initiation of GH treatment and repeated when clinically indicated.

Glucose metabolism. Reduction of insulin sensitivity is a physiologic effect of GH, however, glucose homeostasis is maintained in the vast majority of patients. Most of the available surveillance data do not demonstrate an increased incidence of diabetes, either type 1 or type 2, associated with GH treatment. There are, however, subgroups of patients (*e.g.* Turner's syndrome, Prader-Willi syndrome, and intrauterine growth retardation) inherently at risk of developing diabetes, and these should be carefully monitored.

Diabetes mellitus is not a contraindication to GH treatment in children, and their diabetic care should follow standard clinical practice (as noted in the section below).

Skeletal disorders. Slipped capital femoral epiphysis, scoliosis, and avascular necrosis can be associated with the underlying disorders that are treated with GH therapy. There is no evidence that these conditions are caused by GH treatment, however, scoliosis may be exacerbated when growth is accelerated.

Interaction with other hormones. There is no compelling evidence that GH treatment has any adverse effect on pubertal development and gonadal function.

GH can affect the metabolism of thyroid hormones and cortisol. These issues are discussed in the section on adult GH replacement, but apply equally to children.

Issues related to non-GH-deficient disorders. Monitoring of glucose homeostasis in Turner's syndrome and glucose homeostasis and lipid profiles in chronic renal failure on GH treatment should be undertaken at intervals determined by standard clinical practice. In those patients with chronic renal failure treated with GH who receive a renal transplant, assessment of graft function and surveillance for the development of malignancy should be carried out according to routine nephrology guidelines.

Safety aspects of GH replacement in adults

Glucose metabolism. The prevalence of diabetes mellitus is increased in hypopituitary adults, and the metabolic actions of GH include insulin antagonism. It is recommended that glucose metabolism be assessed in all patients before and during GH replacement. Diabetes mellitus or impaired glucose tolerance is not a contraindication to GH replacement. The care of diabetes in GH-replaced adults should follow standard guidelines, but intensified monitoring of metabolic control is advocated in the early phase of GH replacement of such patients. Eye examination is indicated in the case of overt diabetes and should be conducted in accordance with standard guidelines. Stable background retinopathy should not lead to discontinuation of GH replacement. The development of preproliferative changes and the presence of proliferative retinopathy are contraindications to GH replacement.

Fluid retention. Symptoms related to fluid retention may be encountered especially in the early phase of GH replacement. This partly reflects a GH-induced, dose-dependent normalization of tissue hydration. Monitoring of hydration during GH replacement should include body weight measurement, patient interview, and clinical examination. A reduction of

the GH dose in the case of persistent symptoms attributable to fluid retention should be considered. Increased awareness of such symptoms and signs are recommended in patients with congestive heart failure.

Interaction with other hormones. GH increases the extrathyroidal conversion of T_4 to T_3 and may as such unmask incipient hypothyroidism. Monitoring of thyroid function should, therefore, be conducted in all patients. GH may decrease serum total cortisol concentrations by decreasing circulating cortisol-binding globulin. GH may also reduce the bioavailability of cortisol through an enhanced net conversion of cortisol to cortisone. Even though the clinical implications for these observations are uncertain, increased awareness of glucocorticoid status is recommended in all patients. The possibility that overt ACTH insufficiency may be unmasked during GH replacement should be considered.

Heart function and lipoproteins. The increased prevalence of cardiovascular disease in active acromegaly cannot be extrapolated to the GH-replaced hypopituitary adult. Hence, monitoring of cardiovascular function should follow the standard of care for the normal population. GH replacement in adults is known to increase serum levels of lipoprotein(a). The clinical implications of this, if any, are uncertain and should be weighed against the beneficial effects of GH replacement on other cardiovascular risk factors. We do not recommend measurement of lipoprotein(a) as a standard procedure in hypopituitary patients.

Cancer risk and tumor recurrence. An increased incidence of certain malignancies (especially tumor recurrence) has been reported in hypopituitary adults, but there is no evidence that it is associated with GH replacement. Current recommendations for cancer prevention and early detection in the general population should be implemented in the GH-treated hypopituitary adult.

There is so far no evidence to suspect that GH replacement influences the recurrence rate or regrowth of pituitary/peripituitary neoplasms, but standard clinical practice requires regular pituitary imaging in patients with a history of pituitary pathology. A baseline scan is recommended in all patients before instituting GH replacement therapy.

Safety aspects of pharmacological GH treatment in adults

GH use in the intensive care setting. The power of placebo-controlled trials has been demonstrated with the intensive care unit (ICU) studies, which showed that mortality was doubled in severely ill patients treated with high doses of GH. These studies have refuted clinical practice beliefs that high-dose GH is beneficial in this situation.

The two placebo-controlled clinical trials, which enrolled 522 patients, demonstrated that mortality was increased from 19% in placebo-treated to 42% in GH-treated ICU patients. These included prolonged stay ICU patients following complications from open heart or abdominal surgery, multiple accidental trauma, or those with acute respiratory failure. Supraphysiological doses of GH (5.3–8 mg or 0.07–0.13 mg/kg per day) were administered. The most common causes of death were multiorgan failure, septic shock, and uncontrolled infections. Baseline patient characteristics, severity of illness, and diagnostic category did not explain the increased mortality.

Pharmacological GH treatments. Any GH treatment other than replacement in those who have GH deficiency should be considered as pharmacological. In specific conditions where pharmacological treatment with GH is being considered, standard safety data should be collected and protocols for new drug development followed. The detrimental outcome of high-dose GH treatment in intensive care patients cannot be extrapolated to other conditions, which may potentially benefit from GH treatment.

At present, it is not recommended that pharmacological GH treatment be initiated in adult ICU patients, and ongoing pharmacological GH treatment should be discontinued if such a patient becomes critically ill.

The ICU trial should not discourage new studies of GH treatment in groups that may benefit from GH. The pharmacological doses used in such controlled trials should be the minimum effective dose for the relevant end point.

GH levels and critical illness. The GH-IGF system is dysregulated in critical illness. It is not known whether this has an effect on outcome in such patients or whether adults with GH deficiency, including those receiving replacement therapy, are at higher risk for adverse outcome when critically ill. GH deficiency in adults and children, however, is frequently part of a more extensive pituitary deficiency including adrenocortical deficiency, which should be considered during critical illness in such patients. There are no data to support discontinuation of appropriate GH replacement in patients receiving intensive care treatment for critical illness, or during a period of less severe illness or in relation to surgery.

Closing remarks

The extensive data, to date, collected on large numbers of children and adults treated with GH indicate that for the current approved indications GH is safe. Nevertheless, this workshop has highlighted a number of areas where ongoing surveillance of the long-term safety of GH replacement is important (cancer, glucose homeostasis, high-dose pharmacological treatment). This will require appropriately designed follow-up studies using adequate epidemiological tools and untreated controls.

Four review papers were prepared for the Consensus meeting, and these are listed below:

1. **Clayton P, Cowell C**. 2000 Safety issues in children and adolescents during growth hormone therapy. Growth Horm IGF Res. 10:306–317.

2. **Cohen P, Clemmons D, Rosenfeld R**. 2000 Does the GH-IGF axis play a role in cancer pathogenesis? Growth Horm IGF Res. 10:297–305.

3. **Swerdlow A**. 2000 Design and interpretation of studies of the risk of cancer and other long-term morbidity and mortality after GH treatment. Growth Horm IGF Res. 10:318–323.

4. **Johannsson G, Jorgensen J**. Safety aspects of GH replacement in adults. Growth Horm IGF Res. 11:2. In press.