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Growth Hormone and Treatment Controversy; Long-Term Safety of rGH

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Abstract The availability of recombinant human growth hormone (rGH) for the treatment of growth disorders has provided an unlimited supply for replacement in patients with growth hormone insufficiency, but also for short stature due to Turner syndrome, renal failure, Prader-Willi syndrome, small for gestational age and idiopathic short stature. Considering the potential for side effects in the use of a growth promoting agent, the community of physicians and pharmaceutical manufacturers developed systematic methods to survey for short- and long-term effects. Recently published data from the National Cooperative Growth Study, managed by Genentech, concluded that GH has a 'favorable profile'. In 2012, results from the European Union's Safety and Appropriateness of GH treatment in Europe (EU SAGhE) study about the long-term mortality in GH-treated patients were published in two separate manuscripts. This review will examine the issue of safety of rGH in order to better inform practitioners as they consider initiation of therapy with patients.

Keywords Growth hormone · Drug safety · Adverse effects

Introduction

Recombinant human growth hormone (GH) has been available for treatment of growth disorders since 1985. At that time, the medical community, and in particular the pediatric endocrine community was reeling with the discovery that persons treated with pituitary-derived GH (extracted from cadavers) had developed the devastating and deadly Jakob-Creutzfeldt disease. Months after physicians had to inform treated patients that they were at risk for this disease and that pituitary-derived GH was unavailable, recombinant GH became available for patients with GH deficiency. Unlike pituitary-derived GH that was in very limited supply, manufactured GH offered the possibility of unlimited supply, and no risk of disease transmission. This possibility buttressed the expansion of GH use in patients with growth hormone sufficiency and short stature due to Turner syndrome, renal failure, Prader-Willi syndrome, small for gestational age and idiopathic short stature. With these actions, GH use expanded from physiologic hormone replacement to pharmacologic, growth-enhancing use. The particularly tragic adverse events of the mid 1980s prompted the pediatric endocrine community to make efforts to systematically survey for short- and long-term effects of GH treatment, even as the community accepted the expanded use of GH and prescribed it to a wider variety of patients. In early 2012, results from the European Union's Safety and Appropriateness of GH treatment in Europe (EU SAGhE) study about the long-term mortality in GH-treated patients were published in two separate manuscripts [1••, 2••]. The data, controversial and thought provoking to anyone who prescribes growth hormone, was partially released to government regulatory agencies in press releases months earlier. This left growth hormone prescribers in the position to address patients concerns and advise them with partial knowledge of the data. To fully examine this issue and its consequences, we will discuss the theoretical risks of growth hormone treatment, prior studies of long-term risks, the SAGhE studies and their

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results, criticisms of the SAGhE studies, the manner in which the data were released, recommendations for patients, and recommendations for future studies.

Patients with acromegaly (growth hormone excess) generally secrete more GH than what is given to patients pharmacologically, but the morbidities experienced by these patients give clues to potential short- and long-term adverse effects of GH treatment. Patients with acromegaly experience glucose intolerance and type 2 diabetes mellitus, edema, joint pains and arthritis, hypertension, sleep apnea, and cardiomyopathy [3]. They may also be at higher risk for cancer, particularly of the colon, with some reports stating that cancer mortality is higher. Acromegaly is also associated with a twofold increased mortality risk [4], with evidence suggesting that normalizing GH levels decreases mortality risk [5]. GH, whether native or injected, acts in large part by stimulating production of IGF-1 in target tissues including the liver. Circulating IGF-1 is mostly derived from the liver and is an indirect measure of growth hormone effect. Therefore epidemiological studies of patients with varying natural IGF-1 levels also give us insight into theoretical long-term risks of GH treatment. Some studies have shown that persons with IGF-1 levels in the upper quartile of normal have a greater risk of breast, prostate, pancreatic and colon cancer [6].

These theoretical concerns and the atmosphere of alarm after the historic link between growth hormone and Jakob-Creutzfeldt disease prompted the formation of post-marketing surveillance programs in the late 1980s. Governmental agencies of some European countries established mandatory registries of all patients started on GH, while in the US pharmaceutical companies, encouraged by the US Food and Drug Administration (FDA), established and maintained registries with participation on a volunteer basis. Some of the registries closed in the mid 1990s, while others continued to recruit patients into the 2000s. Data from these programs have provided information about the incidence and temporal occurrence of short-term adverse effects of GH treatment, such as benign intracranial hypertension, slipped capped femoral epiphyses, and worsening scoliosis. Data collected over 20 years from the National Cooperative Growth Study (NCGS), managed by Genentech, was recently published. Data encompassed approximately 55,000 patients treated with growth hormone, representing approximately 200,000 patient-years of treatment [7••]. All indications for growth hormone treatment were included in the analysis. Of 174 cited deaths, 19 were reported to be related to GH treatment, 12 of which were neoplasms. The causes of the other seven deaths varied from overdose to the sudden death associated with Prader-Willi syndrome. There were 29 cases of confirmed new onset-malignancies in treated children, with an expected incidence of 26 cases, given an incidence ratio of 1.12; but the numbers were too low to establish significance. The authors concluded that GH has a 'favorable profile'. Critics of this data recognize the effort and expense to maintain these large registries, and the value of the gathered data, however, they caution that the registries depend upon volunteer enrollment which is subject to bias, upon physician report of adverse events which is subject to underreporting, and that they only monitor patients during the length of treatment, not long enough to detect adverse events that may occur in the longer term [8]. In general the short term risks observed since 1985 are relatively rare, and far less than what was anticipated from experience in patients with acromegaly.

The risks of developing neoplasia have been separately and intensively studied. In the late 1980s, there was a report of an increased incidence of leukemia [9] but these observations have not been noted in subsequent studies and have not been observed in the registries [7••, 10, 11]. Children with primary neoplasms subsequently treated with GH are a particularly closely monitored group because their risk of secondary neoplasm may be higher than normal children. Through an examination of 361 of these children an average of nine years after GH start and comparison with other cancer survivors not treated with GH, the relative risk of developing a secondary neoplasm was found to be 2.15, most commonly for meningiomas [12]. Those with leukemia were at the highest risk of secondary neoplasm, and the recurrence rate of the primary cancer was not different between treated and untreated subjects. No increased risk of recurrence was noted in other studies [13, 14] with smaller populations and longer follow-up.

The risks of developing neoplasia in patients treated with GH without a history of cancer vary between studies. A study of 1,848 persons who received pituitary-derived growth hormone revealed 14 cases of cancer, higher than experienced by the general population [15]. The average length of follow-up was 21 years. After excluding patients at high risk of cancer development, the incidence of colon cancer and Hodgkin's disease remained significantly higher [15]. The authors acknowledged that low numbers of the study (two patients developed colon cancer) precluded firm conclusions about the risks of cancer development after growth hormone therapy but warned that caution should be used. An increased cancer risk, but not colon cancer was seen in 6,272 US patients treated with pituitary-derived GH after a similar follow-up period [16]. In this study, an increased risk of death from adrenal insufficiency was noted, underlying the fact that GH-treated patients often have other comorbidities such as panhypopituitarism that increase their risk of death. After four years of follow-up, 6,840 adults who received recombinant GH for hypopituitarism did not have an increased risk of cancer [17]. These studies underscore the concern for increased risk of cancer in GH-treated persons, but also demonstrate that cancer risk and mortality risks are difficult to assign to GH therapy, as occurrences are

relatively uncommon, even in relatively large data sets. Additionally, individual comorbidities are frequent causes of morbidity and mortality in GH-treated persons.

Recognizing the limitations of volunteer registry data, the European Union's Safety and Appropriateness of GH treatment in Europe (EU SAGhE) study was established in 2009 to gather long-term data on patients initially enrolled in registries between 1985 and 1997. Many of the participating countries established mandatory national registries in 1985 that enrolled all children who began treatment with growth hormone, thus avoiding the biases of volunteer registries. The objectives of the SAGhE study were to investigate long-term efficacy of GH, the long-term mortality and causes of mortality in individuals treated with GH, and the incidence of cancer in individuals treated with GH (http://saghe.aphp.fr/site/).

Available data from the SAGhE studies on long-term mortality of patients treated with GH were published in the February 2012 issue of the Journal of Clinical Endocrinology and Metabolism with data from France published separately from data of other participating countries, Belgium, Sweden, and the Netherlands [1••, 2••]. Data presented in both studies included patients diagnosed with isolated growth hormone deficiency, idiopathic short stature, or small for gestational age, as these diagnoses were deemed to confer a 'low risk' of comorbidity and mortality. In France, of the 6,928 patients included, 93 deaths occurred in the 17 years of follow-up. The number of deaths were more than the 70 expected giving a standardized mortality ratio (SMR) of 1.33. Interestingly, there was no increased risk of neoplasms (SMR 1.03), but an increased risk of cerebrovascular disease, most notably of hemorrhages (SMR of 6.66, with four reported cases). For 21 of the 93 deaths, a cause could not be determined from available records. Causes of death were determined from death certificates, and the French general population was used as the reference for determining SMRs. Seventy-five percent of the 6,928 patients were categorized as having isolated GH deficiency, while 13 % had idiopathic short stature and 5 % were small for gestational age. Thirty-four percent of the patients, not considering the diagnostic indication for GH, were small at birth. The risk of death increased significantly with the use of GH doses greater than 50 ug/kg/day (SMR of 3.41). After adjusting for sex and height, the SMR associated with the higher dose was 2.79 when compared to individuals who received the lowest GH dose. Data from 2,543 persons from Belgium, Sweden, and the Netherlands with the same underlying diagnoses also became available. Twenty-one deaths were reported, with 16 (76 %) of these deaths by accident or suicide. There were no deaths from cerebrovascular disease or neoplasia. Because of the low number of patient deaths, SMRs could not be accurately determined and were not calculated.

These results are thought provoking and prompted many commentaries from the pediatric endocrine community [18–20]. The data from France was criticized because the expected mortality cases were extracted from the general French population, rather than from untreated short persons with similar diagnoses. This criticism is especially salient as persons born small for gestational age have other known morbidities, and persons with idiopathic GHD may have other unknown morbidities. The persons receiving the higher dose of GH generally had a diagnosis of SGA-related short stature, so other morbidities related to this condition may be a factor in the increased risk of death associated with use of higher GH doses. This study is the first to find that persons treated with GH had a higher incidence of cerebrovascular events. Persons with acromegaly are at higher risk of cerebrovascular deaths, with those that received radiotherapy as treatment at highest risk [21]. Interestingly, those with hypopituitarism are also at higher risk for cerebrovascular deaths [22], thus it is unknown whether the increased risk seen in acromegaly is due to the growth hormone disturbance or the oft associated hypopituitarism. Of note, the association between growth hormone treatment and cerebrovascular death was not seen in other countries participating in SAGhE.

Markers of GH efficacy, such as final height or estimated height gain, were not reported. Thus, evaluation of this data from a risk/benefit perspective could not be done. Final height data on a smaller cohort of the French patients were published earlier, and indicated that final height in patients taking GH until final adult height was not significantly different from patients who ended treatment before the epiphyses were closed, putting into question the efficacy of GH and/or the accuracy of the diagnosis of GH deficiency [23].

The manner in which these data were released and shared with the GH prescribing community was not typical and caused some consternation. On September 10, 2010, the European Medicines Agency (EMS) and the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) published press releases stating that a review of somatropin is "being initiated further to information received from the French medicines agency on a long-term epidemiological study … suggesting an increased risk of mortality with somatropin therapy compared to the general population" (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001160.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1). Translated from French, the AFSSAPS release provided more information: "Early results indicate a risk of mortality from all causes compared with the general population (93 deaths observed in this cohort against 70 estimated in a reference population in France). This risk is particularly increased in patients

who received high doses beyond those recommended … The data show no increase in overall cancer mortality (all cancers combined). They suggest an excess mortality associated with the occurrence of cerebrovascular complications (such as intracerebral hemorrhage) and bone tumors" (http://ansm.sante.fr/S-informer/Presse-Communiques-Points-presse/Hormone-de-Croissance-synthetique-somatropine-recombinante-Premiers-resultats-de-l-etude-epidemiologique-sur-la-tolerance-a-long-terme-Communique). On December 22, 2010, the United States Food and Drug Administration (USFDA) released a statement stating "FDA is informing the public that results from a study conducted in France … found that persons with certain kinds of short stature (idiopathic growth hormone deficiency and idiopathic or gestational short stature) treated with recombinant human growth hormone during childhood and who were followed over a long period of time, were at a small increased risk of death when compared to individuals in the general population of France" (http://www.fda.gov/Drugs/DrugSafety/ucm237773.htm). All press releases stated that available information on the risk was under review by the respective agencies. These actions by the regulatory agencies raised public alarm, and prescribers of growth hormone could not adequately address the concerns of patients because released information was incomplete and occurred prior to publication of a peer reviewed manuscript. Interestingly, the principal investigator of the French study released a statement on the SAGhE website that stated, "In practice, we have communicated with our former and current growth hormone-treated patients, as well as with our colleagues in France [about these results. And express] our regrets that communication by the drug agencies was carried out against the opinion of the investigators and in a non-coordinated fashion" (http://saghe.aphp.fr/site/). In the absence of the data, the Pediatric Endocrine Society, based in the US, urged that "members discuss the FDA safety alert with their GH-treated patients and families. This recommendation reflects a consensus that direct and prompt physician-to-patient communication about the issuance of an FDA safety alert regarding hGH treatment is appropriate" (http://www.pedsendo.org/NewsAlert/alert22.cfm). The full results of the study, after peer review, were published in February 2012, 14 months after the initial press releases.

How does one put this data into perspective for everyday practice? Within the pediatric endocrine community, the diagnosis of GH deficiency and GH prescribing practices vary widely, however, the results of the French study have not significantly changed prescribing practices. Providers that are rigorous in their diagnosis of GH deficiency and conservative in prescribing GH continue to be so, citing the French study and other possible unknown risks. Providers who use a broader criterion for the diagnosis of GH deficiency and are more liberal in their prescribing practices of GH cite the excellent safety profile with decades of use and the limitations of the study. Despite these differences in interpretation of the criteria for GH therapy and prescribing practices, practitioners have a professional obligation to understand the limitations of the data sets and present the rationale for GH therapy to patients in a nonbiased manner.

In our discussions with patients about GH therapy, we present the benefits of GH and the commitment that therapy requires. We state that GH therapy improves stature but many years of therapy is needed for maximal benefit to reach adult height, that GH treatment continuation in those with adult GH deficiency is a possibility, that the costs of treatment to third party payers is high, and that contact with physicians for therapy monitoring is frequent, at least three times yearly. We also mention potential improvements in motor development, strength, and body fat as benefits of GH treatment. In presenting the risks of GH therapy, we review the excellent safety record of GH use, the known side effects, including minimal pain at the injection site, rare occurrences of increased intracranial pressure, slipped capital femoral epiphysis, scoliosis progression, edema, and pancreatitis. We present GH as a growth promoting agent with theoretical risks of increasing cancer and diabetes, and emphasize that there is no conclusive evidence of an increased cancer or diabetes risk in patients receiving GH. In discussing the new data with patients, we mention the studies and the increased risk of cerebrovascular disease in one patient population but not the others, and the strengths and criticisms of the study. As this is a lot of information to present at a patient visit, a supplemental handout is useful.

As with any medication, there are inherent risks of long-term morbidities that must be documented and evaluated. Hence, we recommend the establishment of lifespan cohorts of all patients treated with rGH. The logistics are indeed complex with studies involving the community of endocrine physicians, the pharmaceutical industry and government agencies. However, the many concerns raised by the previous studies warrant responsible surveillance in order that physicians who treat patients with growth disorders are properly informed as they make therapeutic decisions with their patients.

Conclusion

Recombinant growth hormone therapy has had an exemplary track record of safety and efficacy. However, several studies have shown that the therapy carries risks of long-term morbidities, some unexplained. Hence, we believe practitioners who prescribe rGH be provided with solid data regarding the long-term safety issues and patients be adequately informed of the benefits and risks related to therapy.

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