Safety of long-term use of daily and long-acting growth hormone in growth hormone-deficient adults on cancer risk

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Daily injections of recombinant human growth hormone (rhGH) have been used in clinical practice for almost four decades as a replacement therapy in adult patients with GH deficiency (GHD). Long-term adherence to daily injections of rhGH is a clinical concern that may result in reduced therapeutic efficacy, and long-acting GH (LAGH) formulations have been developed in an attempt of overcoming this problem. Long-term safety issues of rhGH are the other side of the coin that has been carefully monitored over the years, particularly related to the proliferative actions of GH that could increase the risk of tumor recurrence or induce the development of new benign and malignant tumors. In this review, we present what is currently known about the cancer risk in GHD adults treated with daily rhGH injections and we discuss the major concerns and responses needed from future surveillance studies regarding the safety of LAGH preparations.

Introduction

The introduction of recombinant human growth hormone (rhGH) in the clinical practice in 1985 coincided with the cessation of the treatment with GH from cadaveric pituitaries initiated in 1956 by Maurice Raben, which was tragically associated with many cases of Creutzfeldt-Jacob disease due to contamination of the human pituitary glands [1]. With the plentiful supply of highly pure biosynthetic rhGH, novel therapeutic indications were tested and approved

beyond the previous limited use in children with severe GH deficiency (GHD), including pharmacological treatment in non-GHD children and replacement therapy in hypopituitary GHD adults [1], [2].

Given the multiple biological actions of GH in the body, the safety of daily subcutaneous injections of rhGH administered before bedtime in both children and adults have been carefully monitored over the last four decades. One of the major concerns is related to the potential risk of pituitary tumor recurrence and development or progression of benign or malignant neoplasms due to the well-known role of GH in inducing signaling pathways for cell growth in experimental and animal models *[3], [4]. In GHD children, already in the first years of the recombinant era, a possible association of daily rhGH therapy with the occurrence of leukemia was raised, and subsequently discarded when patients with known risk factors for leukemia were excluded from the analyses and final results demonstrated a cancer incidence not different in rhGH users than in the general population [5]. In adults, pituitary and peri-sellar tumors or their treatment with surgery or radiotherapy are responsible to approximately two-third of cases of GHD, and some of the patients harboring these tumors may present an inherent elevated risk for malignancies, unrelated to rhGH therapy [6]. These facts highlight the care it should be taken in evaluating the risk of tumor progression or cancer in individuals treated with rhGH due to the presence of several confounding factors *[3], [4], *[5], [6].

With the idea of reducing the physical and emotional burden associated with daily subcutaneous injections of rhGH, various long-acting GH (LAGH) formulations have been tested over the years and few are now approved by regulatory agencies and marketed *[7], *[8]. In the clinical trials, therapeutic adherence and patient acceptance were improved with LAGH, with short-term efficacy and profile of adverse events very similar to what is observed in the treatment with daily injections of rhGH [9]. Nevertheless, LAGH therapy results in a non-physiological hormone rhythm that raises new clinical issues, particularly related to doses, monitoring, and long-term therapeutic outcomes *[7], *[8].

In this review, we have summarized what is currently known about the cancer risk in adults treated with daily subcutaneous rhGH injections and we present the major concerns and required responses from future surveillance studies regarding the cancer risk in adult GHD patients treated with LAGH preparations.

In his article published in 1962, describing the first case of cadaveric pituitary-derived GH therapy in an adult with hypopituitarism, Maurice Raben wrote: "*Replacement therapy with thyroid, adrenocortical hormone and estrogen in females or androgen in males is usually satisfactory treatment for adult hypopituitarism. One patient, a thirty-five-year-old female school teacher, treated in this way for eight years, was treated in addition with HGH, 3 mg, three times a week. After two months of HGH she noted increased vigor, ambition and sense of well-being. Observations will be needed in more cases to indicate whether the favorable effect was more than coincidental*" [10]. It was only in the recombinant era, twenty-seven years after Raben's quote, that novel findings on rhGH replacement in adults began to emerge from two pivotal trials [11], [12]. In the following years, a syndrome of GHD in hypopituitary adults was defined and many guidelines from different organizations for its appropriate diagnosis and treatment were published [13]. Evidence from numerous observational studies, controlled trials, systematic reviews and meta-analysis over the last decades favor the beneficial effects of daily rhGH in adults with GHD, a therapeutic modality that is currently approved in most countries. Nevertheless, some controversies still persist on particular issues [14], which might explain the reported variability among countries in the management of adult GHD patients [15].

There have been abundant literature addressing the rationale of the association between GH and the risk of cancer, and a complete survey of this topic is beyond the scope of this article (see references 3–6 for an overview). Thus, the focus of this review is to answer, in the light of current knowledge, whether prolonged treatment with rhGH in GHD adults increases the risk of tumorigenesis.

In 2021, the Growth Hormone Research Society held a consensus workshop with 55 international experts from 16 countries representing 10 professional societies,

with the aim of addressing the safety of rhGH therapy in survivors of cancer and intracranial tumors and in patients with cancer predisposition syndromes [16]. Regarding rhGH replacement in GHD adults, the main conclusions of the panel were (Table 1): [I] the therapeutic effect on secondary neoplasia risk is minor compared to host- and tumor treatment-related factors; [II] studies on tumor recurrence in cancer survivors treated during adulthood are scarce, but current safe-related data are generally reassuring [III] therapy should be discontinued if clinically significant tumor progression or relapse is observed; [IV] patients harboring pituitary tumor or craniopharyngioma remnants should be treated and monitored in the same way than those not treated; [V] there is a contra-indication for therapy in GHD patients with active malignancy, but rhGH might be considered in adult cancer survivors (either with childhood or adult-onset cancer) in remission after careful risk/benefit analysis by the endocrinologist, the patient, and the oncologist; [VI] GHD patients with breast, colon, prostate, or liver cancer should be in remission for at least 5 years and therapeutic decision should be individually based and shared with the oncologist [16].

More recently, safety data from 15,809 GHD adults treated with rhGH (Genotropin®) with a mean follow-up of 5.3 years, who were registered in the Pfizer International Metabolic KIMS Database, were reported [17]. Treatment-related adverse events occurred in 18.8% of the cohort and did not correlated with rhGH dose. Pituitary tumor recurrence was observed in 2.7% of patients, and in 1.3% of them it was considered related to rhGH therapy. Serious adverse events (SAEs) were noted in 25.3% of the patients, and in 4.3% of the cases were related to the treatment. Again, pituitary tumor recurrence was the most frequent SAE, corresponding to 2% of all SAEs and 1% of those linked to the rhGH replacement. Similar or even higher percentages were previously observed in the Hypopituitary Control and Complications Study (HypoCCS), in which tumor recurrence rates were documented in 3668 rhGH-treated and 720 untreated patients with pituitary adenoma, and in 956 rhGH-treated and 102 untreated patients with craniopharyngiomas, showing no influence of rhGH therapy in the risk for recurrence of pituitary adenomas or craniopharyngiomas [18].

In the KIMS study, de novo cancers were diagnosed during the follow-up in 471 of 14,533 (3.2%) patients who did not have a history of cancer at start, being the prostate cancer the most frequent (n = 86), followed by nonmelanoma skin (n = 57), breast (n = 39), lung (n = 37), brain (n = 29), melanoma (n = 25), colon (n = 20), and various other malignancies. In 15 of those 471 (3.2%) patients, a second cancer of different types and at different body sites developed [17]. The risk of cancer in adult-onset and childhood-onset GHD patients receiving rhGH therapy was not different from that observed in the general population, and it was within the expected range according to gender, disease onset, prior rhGH treatment status and pituitary irradiation, and mean GH dose [17]. Of note, de novo cancer incidence in patients with idiopathic/congenital GHD was significantly lower compared to the general population, whereas it was increased in patients who were 15–24 years of age at baseline or attained age of 25–34 years during follow-up. Accordingly, in the HypoCCS study, there was no increased risk for all-site cancers in rhGH-treated patients compared to the untreated group [18]. Taken together, these results suggest that other factors related to the primary pituitary disease might contribute more to carcinogenesis than rhGH therapy per se in GHD adults.

Age is one of the most important risk factors for developing cancers. Recently, effectiveness and safety data of rhGH therapy in GHD adults older than 60 years followed for 10 years were obtained from two observational, noninterventional, multicenter registry studies: NordiNet® International Outcome Study (IOS) and the American Norditropin® Studies: Web-Enabled Research (ANSWER) Program [19]. In these registries, adverse events considered related to rhGH therapy either by the investigator or the sponsor were defined as serious adverse reaction (SAR) or non- serious adverse reaction (NSAR), whereas those unrelated to the rhGH were defined as SAEs. The clinical outcomes of rhGH replacement in older GHD patients were similar to those observed in younger patients, with the incidence rate of SAEs – but not SARs – significantly higher in the older group [19]. Benign, malignant and unspecified neoplasms were the most common SAEs in both groups, corresponding to 1.3% in the middle-aged patients and 1.99% in the older ones. Interestingly, benign, malignant and unspecified neoplasms were also the most common SAR in the middle-aged patients (0.77%), but not in the older group, with approximately 50% of them related to a recurrence of the pituitary adenoma. Only two cancer-related deaths (metastatic colon cancer and anaplastic astrocytoma), both in the younger group, were considered possibly

related to rhGH treatment. Among 652 GHD patients older than 60 years analyzed in the IOS and ANSWER databases, there was only one case of neoplasm (0.15%) reported as SAR [19]. These findings differ from previously reported data obtained from KIMS Database, in which adverse events related to glucose metabolism, cardiovascular events and neoplasms obtained from 295 patients aged > 65 years were more frequent in comparison with 2469 patients aged < 65 years with adult-onset GHD [20]. These conflicting results were mainly due to differences in methodologies, in the studied populations, age and/or more intense surveillance of older patients, rather than to the rhGH therapy itself.

Premature mortality and decreased life expectancy due to vascular complications have been consistently observed in hypopituitarism, whereas lower, increased or not increased standardized mortality rates (SMR) due to malignancies have been reported in hypopituitary patients compared to the general population [21], [22]. Several factors might explain these conflicting data, including the low absolute number of malignancies observed in the cohorts, differences in the control populations and in the prevalence of specific cancers among them, inherent increased risk of malignancy in patients harboring pituitary adenomas, and differences in therapeutic approaches, such as radiotherapy and pituitary hormone replacement [22].

The impact of GHD and rhGH replacement on mortality in hypopituitary patients has been widely debated. Evidence based on observational studies and meta-analysis show that mortality in children or adults treated with rhGH is not increased, with some studies showing reduced SMRs in GHD patients receiving rhGH therapy compared to GHD untreated patients [22], [23], [24], [25], [26]. However, recent data from the Safety and Appropriateness of Growth Hormone treatments in Europe (SAGhE study) have alerted to the increased mortality associated with rhGH therapy in certain groups of patients with an inherent risk related to the underlying diagnosis [27]. In this study, mortality from neoplasms was not increased in patients stratified in risk group 1a, that included individuals treated in childhood due to isolated GHD, idiopathic short stature or mild skeletal dysplasia (SMR 0.9; 95% CI 0.4–1.8), and in risk group 1b, including children who were born small for gestational age (SMR 0.6; 95% CI 0.1–2.4). In contrast, mortality was significantly increased in patients stratified in risk group 2 (multiple pituitary hormone deficiency, severe cerebral and extracerebral

malformation, severe chronic paediatric diseases, long-term steroid use in chronic inflammatory diseases, benign pituitary tumors, Cushing's syndrome, and defined genetic diseases, such as Neurofibromatosis type 1, Turner, Noonan, and Prader-Willi syndromes) with SMR of 2.4 (95% CI 1.4–4.1), and also in risk group 3 (all malignancies, Langerhans cell histiocytosis, chronic renal failure, after bone marrow or solid transplantation, and syndromes with known increased risk for malignancies, such as Bloom, Fanconi, and Down syndromes, and chromosomal breakage) with SMR of 117.3 (95% CI 105.4–130.6). These data clearly demonstrated that while the use of rhGH is safe in most circumstances, its indication must be extremely judicious and even contraindicated in very high-risk individuals [3].

LAGH consists of a group of compounds with distinct pharmacokinetic and pharmacodynamic characteristics that prolong GH actions and can be administered at weekly, bi-weekly or monthly intervals. They are manufactured using different technologies and, therefore, what is observed with one product in relation to its efficacy, safety and monitoring, does not necessarily apply to another LAGH *[7], *[8]. Thus, it is essential to know exactly the properties of each LAGH and how they work in different clinical scenarios. Approval for LAGH varies from country to country and some have only been authorized for therapy in children with GHD [28].

One of the main expectations for the use of LAGH in clinical practice is to improve treatment adherence by reducing the discomfort of daily subcutaneous injections of rhGH. In adults with GHD, hormone replacement is an extended or even lifetime therapy and various studies have implicated daily rhGH injections as a potential barrier for optimal outcomes [29], [30], [31]. After previous unsuccessful attempts, the first LAGH, somapacitan (Sogroya®; Novo Nordisk, Denmark), was finally approved in United States in 2020 and in Japan and European Union in 2021, for replacement therapy only in adults with GHD [28], *[32].

Somapacitan is produced by replacing a single amino acid (Leu101Cys) in a site of the GH molecule not involved with receptor binding. On this modified amino

acid, an acyl group is attached allowing the binding of albumin, which in turn reversibly binds to endogenous albumin, resulting in a prolonged half-life that allows once-weekly subcutaneous administration of the drug *[7], [28]. The approval of somapacitan was based on three pivotal phase III multicenter clinical trials in GHD adults followed for up to 86 weeks that demonstrated its superiority over placebo, and non-inferiority in comparison with daily rhGH, with similar safety profile without new adverse events, and considered more convenient by most patients [9], [33], [34]. In virtue of the differences between the two therapeutic modalities, a treatment guide was recently published with recommendations for physicians initiating treatment with somapacitan in either naïve adult patients with GHD or in those switching from daily rhGH, including dose titration, clinical monitoring, and appropriate timing for measurements of serum insulin-like growth factor-I (IGF-I) [32].

Obviously, given the short period of time since its introduction in the clinical practice, there are no data available on the risk of benign and malignant tumors in patients treated with somapacitan, as well as with others LAGH. However, long-term observational and post-marketing surveillance studies are already underway to clarify this and other questions, similarly to the long-term monitoring that has been conducted with daily rhGH therapy over the years [28], *[32].

There are specific concerns regarding LAGH therapies and increased risk of cancer, particularly in individuals presenting with cancer predisposition syndromes, cancer survivors with childhood-onset GHD and patients subjected to radiotherapy for brain tumors [3]. Recent experimental studies have suggested the involvement of endocrine and/or paracrine GH in promoting a “field cancerization” that creates a pro-tumorigenic environment, favoring neoplastic growth by suppressing tumor suppressor proteins and altering DNA damage repair [35]. In addition, an association between serum IGF-I levels at high-normal range with elevated risk of malignancies, such as receptor-positive breast cancer in postmenopausal women, prostate cancer, thyroid carcinoma, low-grade gliomas and acoustic neuromas, have been shown by epidemiological investigations in the general population [36], [37], [38], [39], [40]. While IGF-I levels are fairly stable 24 h after a daily rhGH injection administered at bedtime in an attempt to replicate the GH nocturnal peaks and daytime through GH

levels, the diurnal pattern of GH is lost with pharmacological therapy with LAGHs and circulating IGF-I profile is modified over the week after injections of somapacitan, with peak levels between day 2 and 3, mean levels between day 4 and 6, and return to nadir levels afterwards *[8], *[32]. These fluctuations may expose body tissues transiently to elevated concentrations of GH and IGF-I, potentially causing metabolic and proliferative abnormalities that would only be noticed after a long period of treatment [7]. These facts highlight the need for careful monitoring in the real-world setting of each LAGH that is commercialized, through well-designed observational studies and large databases from each manufacturer.

Daily injections of rhGH have been used since the mid-1980 s in order to ameliorate abnormal manifestations of hypopituitary GHD adults that include visceral obesity, reduced muscle strength, bone mass and exercise capacity, dyslipidemia, fatigue, poor quality of life and cardiac dysfunction [2]. Considering the multiple biological effects of rhGH in the body and given the lifetime perspective of replacement therapy in GHD adults, continuous monitoring of its therapeutic benefits and risks is essential. Up to now, rhGH therapy in GHD adults has proved to be safe regarding cancer risk when used as recommended by guidelines, respecting the contra-indications and taking special care in high-risk populations [13]. LAGH are coming to clinical practice to offer greater comfort to patients, but the diversity of post-injection hormone profiles related to each LAGH preparation adds unprecedented complexity to the therapeutic regimen. Somapacitan is the first LAGH approved for treatment of GHD in adults, with similar efficacy and adverse events than rhGH in the clinical trials. At long-term, however, the safety of somapacitan as well as of other LAGH, including cancer risk, will only be known with continuous monitoring over the next years.

Practice points

1)
Daily injection of subcutaneous rhGH is a safe replacement therapy in GHD adult patients in relation to cancer risk

2)
rhGH is contra-indicated in GHD patients with active malignancy and may be used in cancer survivors in remission after careful risk/benefit analysis
3)
rhGH therapy should be discontinued if any clinically significant tumor progression or relapse is observed
4)
Somapacitan is the first LAGH formulation approved for treatment of GHD in adults with efficacy and safety profiles comparable to rhGH

Research agenda

1)
Continuity of observational studies and databases in adult GHD patients treated and not treated with rhGH
2)
Implementation of new safety registers for long-term follow-up of patients on treatment with each LAGH preparation
3)
Special attention in monitoring the risk of cancer in older GHD patients, in those with a tumoral etiology of the hypopituitarism or treated with radiation, with cancer predisposition syndromes or in cancer remission, treated and not treated with rhGH or LAGH

Section snippets

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