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Review

Association between growth hormone therapy and mortality, cancer and cardiovascular risk: Systematic review and meta-analysis

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ABSTRACT

Objective: The potential involvement of growth hormone therapy in tumor promotion and progression has been of concern for several decades. Our aim was to assess systematically the association between growth hormone therapy and all-cause, cancer and cardiovascular mortality, cancer morbidity and risk of second neoplasm mainly in patients treated during childhood and adolescence.
Design: A systematic review of all articles published until September 2013 was carried out. The primary efficacy outcome measures were the all-cause, cancer and cardiovascular standardized mortality ratios (SMR). The secondary efficacy outcome measures were the standardized incidence ratio (SIR) for cancer and the relative risk (RR) for second neoplasms. The global effect size was calculated by pooling the data. When the effect size was significant in a fixed model we repeated the analyses using a random model.
Results: The overall all-cause SMR was 1.19 (95% CI 1.08–1.32, $p < 0.001$). Malignancy and cardiovascular SMRs were not significantly increased. Both the overall cancer SIR 2.74 (95% CI 1.18–5.41), and RR for second neoplasms 1.99 (95% CI 1.28–3.08, $p = 0.002$), were significantly increased.
Conclusion: The results of this meta-analysis may raise concern on the long-term safety of GH treatment. However, several confounders and biases may affect the analysis. Independent, long-term, well-designed studies are needed to properly address the issue of GH therapy safety.

1. Introduction

The growth promoting action of growth hormone (GH) is mainly mediated by IGF-I, which, in combination with the GH-independent IGF-II, exerts its actions on the cells in endocrine, paracrine and autocrine manner. The signaling transduction cascade induced by the binding of IGFs mainly to the IGF-I receptor, eventually leads to a potent stimulation of cell proliferation and survival [1]. Due to their anti-apoptotic and mitogenic effects, the role of IGFs in cancer growth and development has been extensively investigated. While there is strong evidence based on experimental data obtained in cellular and animal models showing a role of the GH-IGF axis in the development, maintenance and spread of tumors, such evidence in humans is weak [2].

Epidemiological studies have shown an association between raised circulating levels of IGF-I and an increased risk of developing certain cancers such as prostate, breast and colorectal neoplasms [3–5]. The association between GH-IGF and carcinogenesis is also suggested by the observation that patients suffering from acromegaly, an endocrine disorder characterized by sustained hypersecretion of GH and consequent increased levels of IGF-I, have a higher risk of developing colorectal and thyroid cancer [6–9].

In childhood, recombinant human growth hormone (rhGH) has been extensively used since 1985 to treat children with short stature secondary to a range of disorders including GH deficiency, Turner syndrome, chronic renal failure, small for gestational age (SGA), Prader–Willi syndrome, Noonan syndrome, SHOX deficiency and idiopathic short stature (ISS) [10]. The experience from many thousands of patient years of treatment demonstrates a good safety record for rhGH. Nevertheless, a few reports have raised concern about the long-term safety of GH therapy. In the 1980s, the potential link between GH treatment and malignancy was suggested by case reports linking GH therapy with leukemia risk [11]. A further detailed analysis of this cohort revealed that most of these patients had concomitant conditions predisposing them to cancer, thus leading to overestimation of the risk of malignancy following GH treatment. Reassuringly, the risk of leukemia was not increased in the National Cooperative Growth study, a large, ongoing cohort study, initiated in 1985, of children treated with GH in the USA [12]. In 2002, a long-term study of subjects treated with human pituitary GH during childhood and early adulthood showed an increased risk of mortality from cancer overall, and from colorectal cancer and Hodgkin disease in particular [13]. These conflicting data suggest that

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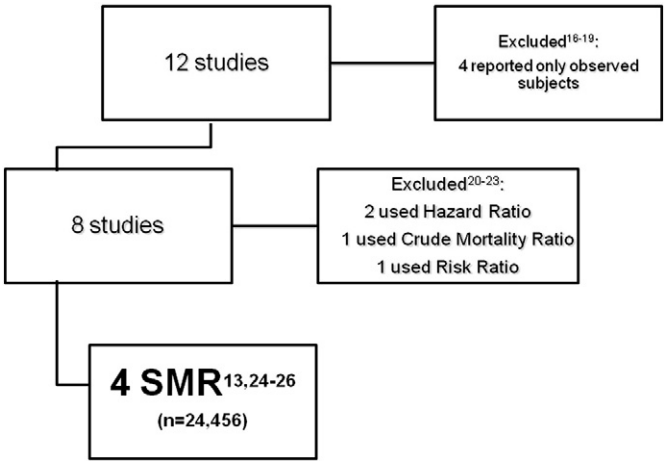

Fig. 1. Search strategy for selection of mortality studies.

long-term surveillance remains crucially important, not only for those being treated with rhGH but also for those who have already discontinued this treatment.

The aim of this systematic review and metanalysis was to examine the evidence that GH treatment during childhood may be associated with a higher risk of all-cause, cancer and cardiovascular mortality and morbidity.

2. Methods

We searched the Medline, EMBASE, ISI Web of Knowledge, and the bibliographic references from all retrieved articles describing such studies up to September 2013 using the search terms "growth hormone" and "rhGH therapy" and "mortality" and "cancer" and "incidence" and "morbidity" and "safety". No language restrictions were applied. Inclusion criteria were treatment with rhGH therapy during childhood and adolescence and long-term follow-up.

2.1. Efficacy outcome measures and quality assessment

The primary efficacy outcome measure was the all-cause, cancer and cardiovascular mortality rate, using the standardized mortality ratio (SMR), defined as the number of observed deaths divided by the number of expected deaths stratified for gender and age in the reference population.

The secondary efficacy outcome measures were the cancer incidence rate, using the standardized incidence ratio (SIR), defined as the number of observed neoplasm divided by the number of expected cases and the risk of second neoplasms, using the relative risk (RR), defined as the incidence of second neoplasms among exposed to GH divided by the incidence among non-exposed.

None of the studies, except one [14], provided raw data on single participants, therefore in the analysis we considered the average values for SMR, SIR and RR and their standard errors.

2.2. Statistical analysis

For primary analysis we calculated the effect size for each study. The effect size was computed as the SMR, SIR, and RR for each trial. We present these scores in a paired analysis with their 95% confidence intervals. Then we calculated the global effect size, pooling the data. When the effect size was significant in a fixed model we repeated the analyses using a random effects model [15]. The random effects model incorporates statistical heterogeneity (results, methods, and publication bias) and provides a more conservative estimate of the pooled effect size than a fixed model. We calculated I^2 values for quantifying heterogeneity in the meta-analysis. I^2 describes the percentage of variability in point estimates that is due to heterogeneity rather than to sampling error. Although no universal rule covers the definitions of mild, moderate, or severe heterogeneity, I^2 values more than 50% indicate notable heterogeneity, whereas values less than 30% indicate mild heterogeneity. We assessed publication bias by funnel plot analysis (see web extras). Analyses were carried out using Review Manager 5 software for Windows package (Nordic Cochrane Centre, Copenhagen, Denmark) and double checked using STATA 12.0 statistical software (StataCorp, TX, USA).

3. Results

3.1. Mortality studies

The search strategy identified 12 long-term studies concerning patient mortality. Eight studies were excluded; four reported observed deaths only [16–19] and four used indices different than SMR[20–23]. Four [13,24–26] out of the 12 studies used SMR rates to evaluate mortality (Fig. 1).

These studies included overall 24,456 patients, with a mean chronological age at study enrolment of 32.6 ± 10.5 years. Mean GH dose in two studies [24,25] was 0.415 ± 0.28 mg/day, while only one study [26] reported a mean dose of 0.024 mg/kg/day. Duration of treatment was reported in only two studies [24,26], with an average of 4.8 ± 4.5 years (Table 1).

3.1.1. All-cause SMR

Van Bunderen et al. [24] reported a significant increase of all-cause SMR in patients enrolled in the Dutch National Registry of Growth Hormone Treatment. The patients were retrospectively monitored and subdivided into three groups: a treatment group (n = 2229), a primary control group (who had not commenced treatment or who had discontinued it before 30 days, n = 109) and a secondary control group (who had endured treatment for more than 30 days but less than 90, n = 356). This cohort included both adult and childhood onset GH deficiency (about 80 vs 20%, respectively). The all-cause SMR was 1.27 (95% CI 1.04–1.56) for the treatment group, 1.42 (95% CI 0.79–2.56) for the primary control group and 1.17 (95% CI 0.82–1.69) for the secondary control group.

Gaillard et al. [25] reported data obtained from the analysis of KIMS (Pfizer International Metabolic Database) including 13,983 GH-deficient patients with 69,056 patient-years of follow-up. The all-cause SMR was 1.13 (95% CI 1.04–1.24). The cohort mainly consisted of patients with adult onset GH deficiency, about 20% showing childhood onset GH

Table 1
Mortality studies with SMR analysis.

Study	Journal	Year	No. of patients	Age at study enrollment (years)	Dose of treatment	Duration of treatment	All-cause SMR	Cancer SMR	CVD SMR
Carel et al. [26]	JCEM	2012	6558	28.3 ± 5.3	0.024 μg/kg/day	3.9 ± 2.6	1.33 (1.08–1.649)	1.02 (0.41–2.09)	3.07 (1.4–5.83)
Gaillard et al. [25]	EJE	2012	13,983	26.9 ± 9.9	0.42 ± 0.27 mg/day	–	1.13 (1.04–1.24)	0.88 (0.74–1.03)	0.83 (0.63–1.08)
Van Bunderen et al.[24]	JCEM	2011	2229	42.6 ± 16.3	0.41 ± 0.28 mg/day	5.7 ± 6.3	1.27 (1.04–1.56)	0.86 (0.6–1.25)	1.35 (0.95–1.94)
Swerdlow et al. [13]	LANCET	2002	1352	–	–	–	–	2.3 (0.8–5)	–