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Human Growth Hormone in IBD: Rationale, Evidence, and Concerns

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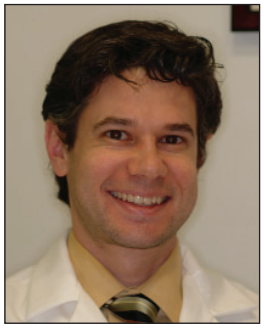

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Human growth hormone (HGH) therapy for inflammatory bowel disease (IBD) may improve disease activity but has been studied in a relatively small number of patients and is not currently approved for the treatment of IBD. While it is approved for children and adults in a limited number of conditions, off-label use in adults is increasingly more common, particularly for anti-aging purposes. Given the panoply of common, rare, and theoretical side effects, it is important that physicians and other health care professionals are aware of the specific indications for growth hormone and its potential for adverse effects, including theoretical concerns for carcinogenesis. This review summarizes the rationale, evidence, and side effect profile for HGH use in IBD.

INTRODUCTION

Human growth hormone (HGH) has been used in children with short stature for over 20 years, and was first studied in pediatric Crohn's disease (CD) over a decade ago (1). HGH promotes growth in pediatric CD, which has been characterized as a GH-resistant state (2). However, in adults there are only a few indications for HGH (Table 1), and it is not approved for the treatment of inflammatory bowl disease (IBD). While HGH was effective in adults with CD in a small, randomized study (3), it has not been investigated in a large controlled trial. In the broader adult population, there has been a recent increase in off-label use of HGH for anti-aging purposes (4). Thus, it is likely that the practicing gastroenterologist or internist will encounter patients with CD who may be coincidentally taking unapproved HGH for anti-aging. We review here published data regarding the use of HGH in IBD, as well as potential side effects of HGH use in various medical conditions.

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DOES HGH IMPROVE IBD?

Growth hormone replacement therapy in IBD patients has primarily been used for the treatment of growth delay in children who suffer from IBD, with variable

Table 1
FDA-approved indications for growth hormone therapy in children and adults. (From the American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children–2003 update (17)).

Approved Indications for GH Treatment in Children
- Growth hormone deficiency
- Turner Syndrome
- Chronic renal insufficiency
- Small for gestational age or intrauterine growth retardation
- Prader-Willi Syndrome
- Continued height deficit at puberty

Approved Indication for GH Treatment in Adults
- AIDS wasting syndrome
- Growth hormone deficiency

effect (1,5–7). Growth delay in children with IBD may be caused by a number of factors, including nutritional status, activity of inflammation, disease severity and genotype, all of which may lead to a GH resistant state (2). There is evidence in both children and adults that suggests that the GH/IGF-1 axis is functionally impaired in patients with IBD. Specifically, IBD is characterized by a state of GH resistance in which there is normal GH secretion but impaired induction of GH target genes (8). GH replacement therefore, may be beneficial by increasing ligand and circulating GH and IGF-1 levels. Furthermore, GH and other trophic factors act upon epithelial cells, mesenchymal cells, and intestinal immune cells to promote improved mucosal integrity, mucosal healing, and modulation of inflammation (9).

There is experimental evidence supporting the use of GH for the treatment of IBD. Studies in rats with chemically induced colitis have shown that GH therapy promotes intestinal mucosal repair (10), and GH has been shown to reduce intestinal fibrosis and stimulate expression of antifibrinogenic signaling molecules (11).

In a placebo-controlled pilot study of 37 adult patients with active CD, GH therapy given concurrently with a high protein diet significantly improved Crohn's Disease Activity Index (CDAI) scores and reduced the need for additional medications. There was a mean decrease of 143 points on the CDAI from baseline values in HGH-treated subjects, as compared with a 19 point drop in the placebo group ($p = 0.004$) (3).

Several clinical trials have also shown that GH has beneficial anabolic effects in patients with short bowel syndrome (SBS), many of whom had CD as an indication for bowel resection. A meta-analysis of 13 trials on 258 patients conducted on the safety and efficacy of growth hormone with a modified high-carbohydrate, low-fat diet in patients with SBS showed a positive treatment effect on body weight, stool output, lean body mass, absorption of carbohydrates, absorption of nitrogen, absorption of D-xylose, and time off total parenteral nutrition in these patients (12).

COMMON SIDE EFFECTS AND SAFETY CONCERNS OF HGH THERAPY

There have been a number of common but benign and self-limited adverse effects reported in clinical studies of GH treatment (Table 2). Common side effects reported in clinical trials include itching and erythema at the injection site, and less common side effects in children such as arthralgia, myalgia, carpal tunnel syndrome, peripheral edema and transient gynecomastia. Rare adverse events have included slipped capital femoral epiphysis, benign intracranial hypertension, scoliosis, pancreatitis and adrenal insufficiency (13).

In one study in adults with IBD, major side effects included edema and headache which generally resolved within the first month of treatment (3). Less common side effects included arthralgia, tender lymphadenopathy and breast tenderness. There were no serious adverse events reported and no patients withdrew from the study because of side effects. Tumors were found in three patients (two treatment, one placebo), which were thought to not be related to GH therapy.

There is a report of an ileal perforation in a patient with Crohn's disease who was receiving recombinant HGH therapy, as well as a report of a patient with ulcerative colitis who developed Cushing's disease while treated with GH due to short stature (14,15).

Most of the clinical trials to date of GH therapy have been performed in adults with adult-onset growth hormone deficiency; in these studies doses of GH treatment are higher than those currently recommended. A systematic review published in 2007 of 18 randomized controlled trials evaluated the safety and efficacy of

growth hormone in the healthy elderly, and showed that persons treated with GH were significantly more likely to experience soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia (16). While diabetes and impaired fasting glucose may occur in the short term, these studies showed that HGH is also associated with reduced fat mass and increased lean body mass.

Other reported side effects of GH therapy in adults include lipoatrophy at GH injection sites, and increased creatinine levels in end-stage renal disease patients (17). Additionally, a study of GH in critically ill European patients showed significantly higher mortality among the GH-treated patients (18). Prior to the use of synthetic GH, there were documented cases of Creutzfeldt-Jakob disease from contaminated human derived pituitary growth hormone (19).

Table 2
Common, uncommon, and theoretical side effects of HGH therapy in adults and children

Common Side Effects of HGH Therapy
- Edema of extremities
- Arthralgia
- Myalgia
- Paresthesias
- Carpal tunnel syndrome
- Headache
- Impaired fasting glucose/impaired glucose tolerance
- Elevated triglyceride levels
- Itching and erythema at injection sites
- Transient gynecomastia

Uncommon Side Effects of HGH Therapy
- Tender lymphadenopathy
- Breast tenderness
- Slipped capital femoral epiphysis (SCFE)
- Scoliosis
- Adrenal insufficiency
- Lipoatrophy at injection sites
- Pseudotumor cerebri
- Benign Intracranial Hypertension
- Ileal perforation (Case report)
- Cushing's disease (Case report)

Theoretical Side Effects of HGH Therapy
- Malignancy (colorectal, prostate, breast, hematologic)

DOES HGH THERAPY CAUSE CANCER?

The most significant theoretical side effect of HGH treatment in IBD patients is the possible increased risk of cancer, which has yet to be definitively established. This theoretical risk is supported by data which shows that GH-stimulated insulin-like-growth-factor-1 (IGF-1) leads to cell growth and inhibition of apoptosis (20). IGF-1 receptors are expressed on human colorectal cancer cells and IGF-1 stimulates the growth of colorectal cancer cells in vitro and has been shown to play an important role in angiogenesis, growth, and metastasis of colon cancer (21).

Much of the potential concern for the role of HGH in the development of cancer stems from findings in patients with acromegaly. Acromegaly is a state of endogenous GH excess, and has been associated with colonic adenomas and colorectal cancer (22). There is some evidence that patients with acromegaly and increased serum IGF-1 have an increased incidence of prostate, breast and hematologic malignancies (23,24). However, these associations have primarily been based on small epidemiologic surveys. Furthermore, the exact role of the GH/IGF-1 axis in the progression from adenoma to carcinoma is unclear. In a cohort study of 1,848 patients with GH deficiency treated with exogenous GH, there was a significant increased risk of mortality from overall cancer, colorectal cancer and Hodgkin's disease (25). However, prospective screening studies of GH replacement in adults have not shown enhanced cancer incidence or mortality (26).

In a 2001 review, The Growth Hormone Research Society concluded that GH therapy is not associated with the promotion of pituitary tumor recurrence or the development of any other neoplasm, and no additional monitoring for other malignant tumors (i.e., prostate, breast, colon) was suggested (27). Furthermore, data from the National Cooperative Growth Study in children showed that long term use of growth hormone was not associated with increased risk of primary leukemia or other malignancies in patients without any preexisting risk factors (13).

In a recent case report, a patient with CD presented with metastatic colorectal cancer within two-years of a normal colonoscopy, while receiving HGH therapy for anti-aging purposes (28). In this report, molecular pro-

files of GH and its signaling molecules were compared in both benign and malignant colonic tissue. Immunoreactivity was more robust in the tumor tissue for insulin-like growth factor-1 receptor (IGF-1R), but not for IGF, GH, or GH receptor. RNA extraction showed that IGF-1R and vascular endothelial growth factor expression were higher in tumor tissue, but not IGF-1, GH receptor or suppressor of cytokine signaling-2 (SOCS-2). These findings support the etiologic role of the GH/IGF-1 axis in the development of colon cancer, and suggest that increased IGF-1 and its signaling molecule VEGF are factors involved in tumor growth. However, these findings do not discriminate between accelerated growth that may be due to increased local GH signaling or circulating levels of IGF-1, nor do they explain whether exogenously administered HGH contributed to the development of *de novo* neoplasia, or stimulated progression of a preexisting neoplasm.

SUMMARY/CONCLUSION

Human growth hormone therapy for IBD may improve disease activity but has been studied in relatively small numbers of patients and is not currently approved for the treatment of IBD. While it is approved for children and adults in a limited number of conditions, off-label use in adults is increasingly more common, particularly for anti-aging purposes. Given the panoply of common, rare, and theoretical side effects, it is important that physicians and other health care professionals are aware of the specific indications for GH and its potential for adverse effects. The use of HGH for approved purposes should be understood in the context of real world application and the theoretical concern for cancer, especially in the IBD patient population already at risk for potential GI malignancies. ■

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