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Growth Hormone Treatment of Growth Failure in Pediatric Patients with Crohn's Disease

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Abstract

Objective—We determined the impact of human growth hormone (GH) injections on growth velocity in growth impaired children with Crohn's Disease (CD).

Study design—Ten children and adolescents (12.6±4.5 years; 6 male) with CD and poor height growth were treated with open label recombinant GH 0.043 mg/kg/day SQ for one year. Patients were retrospectively matched with untreated patients (3 comparisons per case) by race, age, sex, and baseline height. Primary endpoint was height velocity; secondary endpoints were disease activity, body composition, and bone density by DEXA scan.

Results—Mean height velocity in GH-treated patients increased by 5.33±3.40 (mean ± SD) cm/yr during the year of GH compared with 0.96±3.52 cm/yr in the comparison group (p=0.03). Height Z score increased in the treated group by 0.76±0.38 compared with 0.16±0.40 in the comparison group (p<0.01), and weight Z score increased 0.81±0.89 compared with 0.00±0.57 (p<0.01). Bone density revealed an increase of the lumbar spine Z score by 0.31±0.33 (p=0.03 vs baseline).

Conclusions—GH treatment increases height velocity and potentially enhances bone mineralization in children with CD. A randomized controlled trial in a large cohort of children is required to determine the ultimate impact of GH treatment.

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Keywords

DEXA; bone density; height; inflammatory bowel disease; osteoporosis

Growth impairment is reported in approximately 40% of pediatric patients with Crohn's disease (CD), often leading to short stature in adults with CD.¹⁻⁶ The etiology of growth failure may be due to one or several factors, including anorexia resulting in decreased nutrient intake, the inflammatory process resulting in excessive energy and protein expenditure and direct cytokine effects on bone, intestinal nutrient losses, growth hormone (GH) resistance with low insulin-like growth factor 1 (IGF-1), and medications, especially corticosteroids. Growth impairment may precede the onset of intestinal symptoms in children with CD, resulting in delayed diagnosis and treatment.⁷⁻⁹

GH therapy was initially reported as a treatment for CD over 20 years ago, with equivocal results.¹⁰ Subsequent trials using human GH therapy in adult patients with short bowel syndrome associated with CD have demonstrated improvement in body composition, growth and intestinal function.^{11, 12} Administration of human GH has been employed in a small number of children with CD and growth failure with conflicting results. Some reports suggest a lack of response in growth and disease activity measurements unless GH is administered in combination with nutritional supplementation, and others report increases in growth velocity and lean body mass, independent of disease severity and corticosteroid usage, in children with CD.¹³⁻¹⁶

We determined the effects of GH treatment on height velocity, body composition and disease activity in a group of children with CD and growth failure.

METHODS

Patients

Ten patients (6 males) with a confirmed diagnosis⁹ of CD based on prior endoscopic, histologic, and/or radiologic findings, unfused epiphyseal growth plates, and/or height below the fifth percentile for age with no evidence of catch up growth (0.5 increase in height Z score) for the year prior to GH treatment were eligible for enrollment. Exclusion criteria included any current hepatic abnormalities, chronic renal disease, history of non-compliance, or preexisting scoliosis with >20% curvature of the spine. The protocol was approved by the UCSF Committee on Human Research and by the UCSF Pediatric Clinical Research Center, where all procedures were performed. Informed consent was obtained from patients and their parents.

Treatment Protocol

Recombinant Human Growth Hormone (GH) (Nutropin®, provided by Genentech Inc, South San Francisco, California) was administered daily by the patient or parent by subcutaneous injection for one year. GH dose was standardized to 0.043 mg/kg/day and adjusted by weight determined at each visit. GH was prepared by diluting each vial containing 10 mg of GH with 5ml of bacteriostatic water, and each vial was used for multiple doses. Each patient's prescribed therapy for CD, including two patients received corticosteroid therapy, was continued as clinically indicated.

Measurements

Patients were admitted to the Pediatric Clinical Research Center at UCSF at baseline and for repeat evaluations at 3, 6, 9, and 12 months to undergo a thorough history and physical assessment, including anthropometric measurements for calculation of body mass index and

body fat mass, and for laboratory tests to assess disease activity (complete blood count, ESR, serum albumin), medication effects (liver enzymes, amylase, BUN, creatinine), nutritional state (serum vitamin B12 and iron, RBC folate, and plasma zinc levels, and fecal alpha-1-antitrypsin clearance), and hormone levels (IGF-1, IGF-BP3, insulin, fasting blood sugar, T4, TSH). IGF-1 levels were standardized for Tanner stage. The Pediatric CD Activity Index (PCDAI) was determined at each visit.^{17,18}

Weight and height were recorded from the medical records of each patient from one year before enrollment. Weight and height were measured at baseline and at scheduled three month follow-up visits for one year. Weight was obtained by digital scale (Scale-tronix™) to the nearest 0.01 kg, and height was measured using a SECA stadiometer to the nearest 0.1 cm. Weight and height measurements were converted to Z scores using CDC data from a Microsoft Excel file previously found at the website:

http://family.georgetown.edu/welchjj/netscut/nutrition/growth_discussion.html.com.

Bone age was determined by wrist radiograph. Bone density and body composition (total body fat) were assessed by dual energy x-ray absorptiometry (DEXA) [Model: QDR 4500A (S/N 45002)].¹⁹ Measurements were taken from the lumbar spine (L1-L4) and hips for bone mineral density (BMD) and of total body density for fat content at baseline and after one year of GH therapy. Age adjusted values were used for comparison and for derivation of Z scores. DEXA and wrist radiographs were done at baseline and after one year of therapy.

A research nutritionist (RD) assessed dietary intake for a five-day period prior to admission to determine daily energy, fat, protein, calcium, and zinc intake. Five-day diet records were analyzed using Food Processor SQL, Versions 9.0–9.6 (ESHA Research, Salem, Oregon).

Selection of matched comparison group

We utilized the PediIBD consortium registry to select the comparison group.⁹ The PediIBD Registry included all consecutively enrolled IBD patients from six nationwide sites, and clinical data were collected (including demographics, height, weight) from January 2000 to November 2003. Of 1736 IBD patients, 989 patients with CD were identified, described previously.²⁰ For each case subject treated with GH, three comparison subjects with CD were retrospectively matched by age, sex, race and height (at baseline age of each matched case) from the Registry. Two of the initial 10 cases enrolled in the GH study were removed from the matched comparison analyses, because suitable baseline matches were not found in our database due to severity of growth delay (6.7 year old male) and age (19.6 year old male). None in the comparison group was treated with GH, but all were receiving standard treatments and nutritional supplements for CD. Patients were selected from the closest three matches for height at the matched age of each case at baseline (N=24). Ages were calculated using birth date data (month and year of birth) and were matched within 0.2 years. Heights were matched within 3.0 cm (mean difference between case and comparisons was 1.3 ± 1.7 for cm and 0.21 ± 0.30 for Z-score). All cases and comparisons had a confirmed diagnosis of CD and were Caucasian.

Statistical Analysis

Data were analyzed by paired Student's t-test to assess differences between baseline measurements and measurements at 1 year in cases and comparison patients. Analysis of variance for repeated measures was applied to assess differences in growth velocity and changes in BMI Z scores between cases and comparisons. STATA 7.0 was used for all analyses. Significance was defined as $p < 0.05$. Data are expressed as means $\pm$ standard deviation (SD).

RESULTS

Treated Patients

Case #1 - 4.8 year-old male—Diagnosed at 3.2 years of age with ileocolonic CD, this patient's only other treatment was an elemental diet and omega fatty acid supplements. At the end of 1 year of GH therapy, his height was 112.4 cm ($Z = -0.33$), showing an increase of 8.1 cm. IGF-1 levels were low (52 ug/L at baseline and 48 ug/L at 1 year) throughout the study; he was the only subject to have a decline in the treatment period. His PCDAI, Tanner Stage, and BMD by DEXA scan did not change during the treatment year. Although his caloric intake was adequate, his dietary calcium intake was only about 50% of the Recommended Dietary Allowance (RDA) at the end of the study.

Case #2 - 6.7 year-old Asian-American male—Diagnosed at 2.8 years old with gastric and ileal-colonic involvement and previously treated with prednisone; at 5 years of age, he had a subtotal colectomy with ileostomy and a Hartmann pouch. At baseline for GH treatment, his medications were prednisone, 6-mercaptopurine, omeprazole, folate, and ferrous sulphate. Within the first two months of GH treatment, he required two hospitalizations for typical relapse episodes. Prior to the 3 month visit he experienced another flare and was restarted on infliximab. He was hospitalized at six months and at nine months when he was started on tacrolimus. Despite his recalcitrant disease and recurrent hospitalizations, he grew 15.1 cm (12.6 cm/yr). At the end of his GH treatment period, he was 7.9 years old, remained Tanner stage 1 and had a bone age of 4.5 years. Because of profound growth delay, a baseline matched comparison could not be found in our database. His IGF-1 levels, which were within normal range for Tanner stage, increased from 143 ug/L from baseline to 338 ug/L after one year of treatment.

Case#3 - 10.7 year-old male—This prepubertal male was diagnosed with ileocolonic CD and had been treated with mesalamine, 6-mercaptopurine and prednisone. DEXA revealed demineralization with increased risk for fractures (lumbar spine Z score = -1.5). During the first two months of treatment, weight measurements were adjusted after weighing his cast, determined to be ~1 kg. He continued taking mesalamine, azathioprine, a multiple vitamin, loratadine, acetaminophen, and glycolax. After 11 months of GH, his height had increased 10.0 cm (10.9 cm/yr). IGF-1 levels were within normal range for Tanner stage and increased by 146 ug/L from baseline to 275 ug/L. He requested adequate calories but <50% of the RDA for calcium per 5 day food diary at the end of the study.

Case#4 -11.5 year-old female—Diagnosed with gastric and ileal-colonic CD, this girl presented with a growth velocity of 1.4 cm/yr for the year prior to starting treatment with GH. Throughout the study period she continued to take azathioprine, mesalamine, an elemental diet as sole source of nutrition every fourth month, and folate, zinc and iron supplements. After one year, she had grown 8.0 cm ($Z = -1.79$). Her IGF-1 levels rose to 251 ug/L at 1 year, remaining below the normal range for Tanner stage. At baseline her intake was <100% RDA for caloric, zinc, calcium and iron intakes, but by the end of the treatment period, she had achieved RDA for all of these nutrients.

Case#5 -13 year-old male—Initially diagnosed at 3.2 years of age, this patient had gastric and colonic involvement and was treated with intermittent prednisone, mesalamine suppositories, and olsalazine for two years. He stopped all medications and remained in remission for six years. At 12.5 years a flare was treated with an elemental diet but required prednisone to achieve remission. Growth velocity prior to initiating treatment was 4.4 cm/yr. Treatment consisted of mesalamine, homeopathic remedy (*Lycopodium*) and supplements with a multiple vitamin, calcium, iron, and folic acid. After one year of GH treatment, he had

grew 14.3 cm ($Z = -1.32$). His IGF-1 levels increased from 357 ug/L at baseline to 735 ug/L at 1 year. At baseline his calcium and zinc intakes were <60% of the RDA; his zinc intake increased to 93% of the RDA by the end of the GH treatment period.

Case#6 - 13.3 year-old female—This girl was diagnosed at 11.4 years old when her appendix was removed and histology revealed granulomas. Follow-up endoscopy and colonoscopy revealed disease in her stomach and ileocolonic areas. During GH treatment, she grew 10.0 cm ($Z = -2.15$). Baseline IGF-1 level was abnormally low (109 ug/L), was 356 ug/L at 6 months, and increased to 467 ug/L by the end of the study. Both her baseline calcium and zinc intakes were 50% of the RDA and 70% of RDA by the end of GH treatment.

Case#7 - 14.1 year-old female—Diagnosed at 12.1 years old, 3 months later she underwent resection of her ileocecal region including the appendix and an incidental Meckel's diverticulum. At initiation of GH treatment, she was taking prednisone, 6-mercaptopurine, and mesalamine. The dose of prednisone was tapered within the first two months of GH treatment. After one year of GH, her height increased 7.4 cm ($Z = -0.77$). Serum zinc was low throughout the study period. Her IGF-1 was within normal ranges throughout GH treatment (414 ug/L at baseline and 468 ug/L at 1 year). Caloric intake was normal, but zinc and calcium intakes were < 60% of the RDA at multiple measurements during the study.

Case#8 - 14.8 year-old female—After presenting with a five year history of symptoms, this girl was diagnosed and treated with a course of prednisone beginning five months prior to enrolling in this GH study. During the study period, she was able to discontinue prednisone within two months and was continued on sulfasalazine, azathioprine, ciprofloxacin, and supplements with folate, calcium and iron. Six months into the study, she continued to complain of daily abdominal pain. Colonoscopy revealed aphthous ulcers and a narrowing in the distal ileum, and she began infliximab infusions. In the 12 months of GH injections, she grew 4.7 cm. Her IGF-1 levels were within normal range, increasing gradually with GH treatment from 350 ug/L at baseline to 845 ug/L at 6 months and 619 ug/L (with six months of infliximab) at 1 year. Dietary intake for iron and zinc met RDA at assessment times, but calcium intake was consistently <85%.

Case#9 - 17.6 year-old male—This patient presented at 15.8 years of age with gastric, ileal and colonic involvement and was initially treated with TPN and antibiotics. At 16.7 years he underwent resection of a transverse colonic stricture and started treatment with azathioprine and metronizadole. During the study he concurrently took azathioprine, a multiple vitamin, vitamin K, and occasional antacids. Four months after beginning GH he developed fever and fatigue and was diagnosed with mononucleosis. Azathioprine was temporarily discontinued for transient leukopenia ($WBC < 2000$). During the year of GH treatment he grew 4.3 cm. IGF-1 increased from 335 ug/L baseline (abnormally low for Tanner IV) to 714 ug/L at 1 year (normal). Serum zinc levels were low throughout the study period despite receiving zinc supplementation. Diet analysis revealed that he took adequate calories, but calcium and zinc intakes were <50% of the RDA.

Case#10 - 19.6 year-old male—Diagnosed at 15.1 years, he underwent partial sigmoid colectomy (15 cm) for perforation following colonoscopy. He had a temporary colostomy, was treated with TPN for 7 months, and then was placed on nasogastric and for a short time gastrostomy-infused semi-elemental formula. He had been treated with two infusions of infliximab. At the start of GH treatment, he was taking mesalamine, prednisone, 6-MP, pentaprazole, Prozac, metoclopramide, and supplements with iron, folate, calcium and multiple vitamins. During GH therapy, he grew 1.9 cm and gained 7.3 kg. IGF-1 levels increased from 279 ug/L baseline (abnormally low for Tanner IV/V) to 748 ug/L at 6 months (within normal

range for Tanner Stage). Serum zinc levels were low at 3 months and doubled at 1 year. His caloric and other nutrient intakes were above the RDA for all time points, except his zinc intake was <70% RDA at baseline.

Overall Results

Baseline characteristics of the patients treated with GH are summarized in Table I. Comparison_{[H2][H3]} patients had a mean age of 12.5 ± 3.7 years, height Z-score of -1.80 ± 0.79 , weight Z-score -1.19 ± 1.22 and BMI Z-score of -0.19 ± 1.21 (Table IV; available at www.jpeds.com). Four of our patients were pre-pubertal and six were peripubertal at enrollment (Table I). Five of the patients had a change in Tanner Stage during the course of the study. The mean height Z score of the nine subjects <18 years of age at baseline was -2.5 ± 1.6 , and their mean weight Z score was -1.9 ± 1.4 . Nine of the 10 patients had bone age less than chronological age at baseline with a mean bone age of 1.9 years below chronological age. End of treatment results are shown in Table II.

Medications and Nutrition

Each patient remained on their individualized clinically-indicated therapies for CD (Table V; available at www.jpeds.com). Comparison patients were also receiving standard treatment regimens (Table VI; available at www.jpeds.com). The nutrition source for patients in the study varied and included temporary TPN (n = 1), elemental formula diet (n=1), and a regular diet (n = 8). Five-day diet records were completed at five standardized time points during the study, and all patients had data from no less than 10 days of intake records available. All patients consumed >85% of the RDA for age for calories.

Body Composition/Bone Density

BMI Z score increased in the cases by 0.46 ± 0.72 (not statistically different from baseline; $p=0.11$). Differences between treated and comparison subjects were also not statistically significant ($p=0.12$). DEXA scans after one year of GH treatment revealed mean increase lumbar spine Z scores of 0.31 ± 0.33 ($p=0.03$) above baseline measurements. Mean percent body fat (by DEXA scan) decreased by 2.55 ± 2.58 ($p=0.03$), suggesting an increase in lean body mass. Mean bone age increased by 0.97 ± 0.95 ($p=0.04$) (from 10.81 ± 3.39 to 12.83 ± 1.66). Serum alkaline phosphatase increased 72.8 ± 50.93 (from 127.3 ± 31.4 at baseline to 200.0 ± 71.3 at end of GH treatment; $p=0.005$).

Measures of Endocrine Status

Mean IGF-I levels increased from baseline to the 1 year follow up period by 225.71 ± 60.68 ug/L (from 249.43 ± 146.80 to 447.13 ± 242.56 ; $p=0.01$). Mean IGF-BP3 levels were within age-adjusted normal ranges for age, although the IGF-BP3 levels increased within the normal range during GH treatment by 0.88 ± 0.66 mg/L, from 2.70 ± 0.54 to 3.58 ± 1.03 ($p=0.001$). Two patients were below normal for Tanner Stage at baseline; one remained below normal after one year of GH treatment. No significant changes were observed in Free T4, TSH, creatinine, Zinc, Ca, Na, K, Cl, and HCO_3 in cases from baseline to the 12 month follow-up period (data not shown).

Growth

Data from GH-treated boys (n=4) and girls (n=4), mean age 12.5 ± 3.7 years (range 4.8–17.6 years), were used for final analysis and for selection of the matched comparison group (n=24). Mean height velocity increased from 3.00 ± 1.39 cm/yr at baseline to 8.32 ± 3.20 cm/yr at 1 year of GH ($p=0.003$). Mean height velocity of the untreated comparison group was 3.98 ± 2.32 at baseline and 4.94 ± 2.85 cm/yr after one year (Figure). The difference in height velocity over the one year period between the treated and comparison groups was significant ($p<0.01$). Case height Z scores increased by 0.76 ± 0.38 , and weight Z scores increased by 0.81 ± 0.89 , while

comparison height Z scores increased by 0.16 ± 0.40 cm and weight Z scores by 0.00 ± 0.57 . ANOVA comparisons of treated and comparison groups also showed significant differences: Z-score for height: $F=8.24$, $p<0.01$ and Z-score for weight: $F=5.90$, $p<0.01$ (Table III).

Disease Status

The PCDAI varied in all patients during the study. The mean PCDAI was 21.9 ± 21.2 at baseline and 13.1 ± 7.5 after 1 year of treatment (mean change = -8.8 ± 17.1 [$p=0.19$]).

Adverse Events

No patient experienced any adverse reactions to the GH. The primary problem encountered with this treatment appeared to be initial reluctance to the injections, particularly among younger children. Within a week, all patients tolerated the injections without difficulty.

Of the two subjects removed from comparison statistical analysis, the 6-year-old subject experienced a worsening of disease that required hospitalization twice during the study. This patient had been refractory to medical management since his diagnosis at approximately 1 year old. However his growth rate was greater than 12cm/yr during GH treatment.

The oldest patient who was excluded from the final analysis due to lack of matched comparison was enrolled into the study for poor growth and open epiphyses on bone age radiograph.

DISCUSSION

These data show that children with CD treated with GH sustain increased height velocity and improved bone mineral density. In contrast, Calenda et al suggested that treatment with GH for 1 year (0.05 mg/kg/d) did not improve growth or nutritional status compared with placebo in CD.¹³ The investigators suggested that this lack of effect may be due to an insufficient dose of GH and that responses were only seen in patients receiving concomitant nutritional support, or in patients with well-controlled disease. Our study was not placebo-controlled, but comparison with a retrospective group of patients matched for height, sex, and age revealed a significant response in growth rate despite varying disease activity (PCDAI), a slightly lower but standard dose of GH, and without specific nutritional support. As in other studies, corticosteroid therapy did not appear to impact GH treatment, although the number of patients in our study is too small to make any conclusion about this observation.^{12,16} Nevertheless, none of our patients required increased use of corticosteroids, and the one patient (#6) taking prednisone was weaned during the course of GH treatment.

A total of 10 other pediatric IBD patients in uncontrolled GH treatment trials have been reported, in two published (3 patients each) and one abstract (4 patients) reports.^{10,14,15} Results vary, with one study showing no growth effect and two showing increased height velocity. None had reported on bone density studies in the course of therapy.

An equally important finding was the enhanced bone density observed in our patients. Bone mineral content is recognized as a significant issue in children with chronic disease. Calcium and vitamin D supplementation has not made any significant impact in this problem, and various protocols are underway to determine whether bisphosphonates will improve the bone mineral content of patients with CD.^{19, 21–25} The observation that GH helps improve bone mineral density suggests GH may be a viable alternative to these other therapies.

Despite persistent growth, our group of patients did not appear to achieve any consistent clinical improvement in their CD activity. Further study is necessary to determine the role of GH as a primary treatment strategy or as an adjunct for growing children and adolescents undergoing treatment with other modalities.

Ideally, advancement in bone age should not exceed the change in chronological age. Although the mean increase in bone age was less than 1 year, 5 of 9 subjects showed an increase in bone age greater than 1 year. Rapid advancement of bone age could potentially lead to compromised adult final height. Due to the heterogeneity of the chronological ages and pubertal stages of the patients in our study, our data cannot be used to determine the significance of the changes in bone age. Thus, well-controlled, prospective, longitudinal trials are required prior to recommending widespread use of GH to treat growth impairment in pediatric patients with CD.

This report has several limitations. Although we were able to utilize a large and robust database to find three matched comparisons for each of the eight subjects in the final analysis, the comparison group is retrospective. The extent and location of disease may influence the response to treatment (i.e. colitis compared with more diffuse or small intestinal involvement). The number of subjects enrolled is too small to control for concomitant medications, including corticosteroids, and nutritional and other supplements. A recent report documents sustained growth among patients with CD treated with infliximab alone, although a role for GH to aid those patients who are growth delayed needs to be systematically investigated in this group of patients.²⁶ Comparison patients were matched for age and sex but not for pubertal stage. The optimal dose and dosing regimen for GH may be different than that employed in this protocol. Additionally, the effects of nutritional factors (e.g., amount of calcium and vitamin D) and activity levels on growth and bone mineralization were not evaluated and need to be considered in future studies.

Despite these limitations, our report suggests that GH can improve height growth in children and adolescents with CD. Furthermore, GH appears to improve bone mineralization and body composition in these patients. Controlled and systematic investigations are warranted to determine the efficacy of GH in treating growth delay as a complication of CD.

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Abbreviations

DEXA

bone density by dual energy x-ray absorptiometry

IGF-1

	insulin growth factor-1
BP3	binding protein-3
T4	thyroxin
TSH	thyroid stimulating hormone
SQ	subcutaneous
GH	human growth hormone
CD	Crohn's disease
IBD	inflammatory bowel disease
ESR	erythrocyte sedimentation rate
6MP	6-mercaptopurine
TPN	total parenteral nutrition
PEG	polyethylene glycol
PPI	proton pump inhibitor

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Figure.

Height velocity (HV) (cm/yr) in 8 pediatric patients with CD at baseline and after six and 12 months of GH treatment and HV in 24 pediatric patients with CD not treated with GH (each line represents the mean of three matched control patients for each patient).

Baseline demographics and laboratory results for the 10 patients (cases) with CD who were treated with GH

Table 1

Case #	Age (Years)	Bone Age (Years)	Sex	Tanner Stage	Age at Diagnosis (Years)	Disease Duration (Years)	PCDAI	ESR (mm/hr)	Zinc level (µg/dL)	Height (Z-score)	Weight (Z-score)	Growth Velocity (cm/yr)	IGF-1 (ug/L)
1	4.8	3.5	M	I	2.6	2.2	20	64	745	-0.71	-0.78	4.0	52
2	6.7	2.7	M	I	2.8	3.9	25	4	662	-6.24	-4.14	3.0	143
3	10.7	11.0	M	I	10.1	0.6	10	2	853	-2.19	0.03	1.0	146
4	11.5	8.5	F	I/III	11.3	0.2	25	20	1085	-2.13	-1.22	1.4	126
5	13.0	12.0	M	II	3.2	9.9	10	12	987	-2.24	-1.93	4.4	357
6	13.3	12.0	F	I	13.4	0.0	70	55	601	-3.61	-3.59	3.0	109
7	14.1	12.0	F	II	11.1	3.0	15	9	556	-1.65	-0.81	3.6	414
8	14.8	13.5	F	III	14.2	0.6	25	28	611	-0.99	-1.88	2.0	350
9	17.6	14.0	M	IV	15.9	1.7	0	12	638	-2.54	-2.56	4.6	335
10	19.6	18.0	M	IV/V	15.1	4.5	5	7	n/d*	n/a	n/a	0.7	279
mean	12.6	10.7			10.0	2.7	21	21	749	-2.48	-1.88	2.8	231
SD	4.5	4.7			5.2	3.0	20	22	187	1.65	1.37	1.4	129

* n/d: test not done

** n/a: Z score not available for age

All subjects were Caucasian except Case #2 who was Eurasian.

Table 2

End of treatment results

Case #	Change in Bone Age (years)	Change in Lumbar DEXA Z score	Change in Height for Age (Z score)	Change in Weight for Age (Z score)	Change in BMI for Age (Z score)	Total change in height (cm/yr)
1	n/d [*]	-0.41	0.38	0.28	0.08	8.1
2	1.8	-0.04	1.60	2.61	0.02	15.1
3	0.0	0.50	0.88	0.13	-0.25	10.0
4	2.3	0.10	0.34	-0.25	-0.63	7.8
5	1.5	0.40	0.92	1.19	0.67	14.3
6	0.0	0.50	1.46	2.42	1.52	10.0
7	1.5	0.60	0.88	0.42	0.02	7.4
8	0.0	0.30	0.59	0.93	0.82	4.7
9	1.5	0.45	0.46	1.56	1.24	4.3
10	-0.8	0.58	n/a ^{**}	n/a ^{**}	n/a ^{**}	1.9
Mean	0.9	0.30	0.83	1.03	0.39	8.4
SD	1.1	0.32	0.45	1.01	0.71	4.2

^{*} n/d: test not done

^{**} n/a: Z score not available for age

Table 3

Analyses of Growth and Body Composition of Treated Cases and Comparison Group (Treated cases n=8; Comparison patients n=24)

Growth	Baseline	1 year	Change	p-value
Case Height Velocity (cm/yr)	3.00 (± 1.39)	8.32 (± 3.20)	5.33 (± 3.40)	p<0.01
Comparison Group Height Velocity (cm/yr)	3.98 (± 2.32)	4.94 (± 2.85)	0.96 (± 3.52)	p=0.20
Case vs Comparison Group:			F=3.58	p=0.03
Case Height Z Score	-1.99 (± 0.90)	-1.24 (± 0.72)	0.76 (± 0.38)	p<0.01
Comparison Group Height Z Score	-1.80 (± 0.79)	-1.64 (± 0.99)	0.16 (± 0.40)	p=0.07
ANOVA Case vs Comparison Group:			F=8.24	p<0.01
Case Weight Z Score	-1.60 (± 1.14)	-0.79 (± 0.47)	0.81 (± 0.89)	p=0.02
Comparison Group Weight Z Score	-1.19 (± 1.22)	-1.19 (± 1.16)	0.00 (± 0.57)	p=0.99
ANOVA Case vs Comparison Group:			F=5.90	p<0.01
Body composition				
Case BMI Z Score	-0.56 (± 0.94)	-0.10 (± 0.55)	0.46 (± 0.72)	p=0.11
Comparison Group BMI Z Score	-0.19 (± 1.21)	-0.34 (± 1.15)	-0.01 (± 0.88)	p=0.41
Case vs Comparison Group:			F=2.20	p=0.12

Table IV

Baseline characteristics of the comparison patients (n=24)

Case # ^{**}	Age (Years)	Sex	Height for Age (Z Score)	Weight for Age (Z Score)	BMI for Age (Z Score)
1	4.8	M	-0.60	0.60	1.52
3	10.7	M	-1.81	-1.40	-0.36
4	11.5	F	-1.69	-1.20	-0.19
5	13.0	M	-2.04	-0.89	0.40
6	13.3	F	-3.21	-2.67	-1.08
7	14.1	F	-1.69	-1.25	-0.70
8	14.8	F	-1.02	-1.14	-0.74
9	17.6	M	-2.32	-1.57	-0.33
Mean	12.5		-1.80	-1.19	-0.19
SD	3.7		0.79	1.22	1.21

^{**} Each Case # is matched with three different comparison patients as described in the Methods section. The age, height for age, weight for age, and BMI for age is the mean of the three comparison patients.

Table V

Medications and supplements taken concurrently during the year of GH treatment

Case #	Concurrent IBD Medications	Supplements	Other GI
1	elemental formula	folic acid, omega fatty acid supplement, herbal supplements, zinc	None
2	6-MP, prednisone, infliximab, TPN	folic acid, iron	PPI
3	5ASA, 6-MP	multivitamin	PEG
4	5ASA, azathioprine, elemental formula	folic acid, iron, zinc	None
5	5ASA	multivitamin, folic acid, calcium, iron, homeopathic supplements	None
6	5ASA, azathioprine	multivitamin, iron, vitamin C, zinc	PPI
7	5ASA, 6-MP, prednisone	multivitamin, folic acid, vitamins B ₁₂ , vitamin E, fish oil, calcium, iron, zinc	H2 blocker
8	5ASA, azathioprine, ciprofloxacin, infliximab	multivitamin, folic acid, calcium, iron, zinc	PEG, H2 blocker, PPI, dicyclomine, probiotics
9	6-MP	multivitamin, vitamin K, calcium, zinc	none
10	5ASA, 6-MP, prednisone, infliximab	multivitamin, folic acid, calcium, iron,	PPI, metaclopramide

5ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; PEG = polyethylene glycol; PPI = proton pump inhibitor

Table 6

Medications and supplements taken concurrently by patients in the Comparison group during the year of growth measurements

Matched Case #	Concurrent IBD Medications	Supplements	Other GI
1	Azulfidine, biaxin	folic acid	none
1	5ASA, flagyl, prednisone	none	none
1	flagyl, prednisone	none	none
2	Azulfidine, flagyl, prednisone	none	none
2	6MP, azulfidine, prednisone	none	H2 blocker
2	azulfidine, prednisone	multivitamin, iron, folic acid	none
3	5ASA, 6MP, prednisone	none	PPI, probiotics
3	5ASA, prednisone	multivitamin	none
3	infliximab	iron	H2 blocker
4	5ASA, prednisone	folic acid	none
4	5ASA	none	none
4	Azulfidine, prednisone	none	none
5	none/unknown	none/unknown	none/unknown
5	prednisone	none/unknown	none/unknown
5	5ASA, 6MP, flagyl, prednisone	none	H2 blocker
6	Azulfidine, prednisone	folic acid	none
6	6MP, azulfidine, flagyl	folic acid	none
6	azathioprine	calcium, folic acid	none
7	5ASA, 6MP	none	PPI
7	5ASA, flagyl, prednisone	multivitamin, iron	H2 blocker
7	5ASA, azathioprine	folic acid	H2 blocker
8	5ASA	calcium, multivitamin, iron, folic acid, zinc	none
8	5ASA, 6MP, infliximab, prednisone	multivitamin, zinc	H2 blocker
8	Azulfidine	none	none
9	5ASA, 6MP	folic acid	H2 blocker
9	5ASA, prednisone	none	none
9	None	multivitamin, iron, zinc	none
10	5ASA, imuran, prednisone	folic acid	none
10	5ASA, 6MP, cipro	multivitamin, folic acid	H2 blocker, PPI
10	6MP, cipro, prednisone	none	none

5ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; PEG = polyethylene glycol; PPI = proton pump inhibitor