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A Multi-Center Controlled Trial of Growth Hormone Treatment in Children with Cystic Fibrosis

Michael S. Stalvey[1], **Ran D. Anbar**[2], **Michael W. Konstan**[3], **Joan R. Jacobs**[4], **Bert Bakker**[4], **Barbara Lippe**[4], and **David E. Geller**[5]

[1]University of Massachusetts Medical School, Worcester, MA, USA

[2]SUNY Upstate Medical University, Syracuse, NY, USA

[3]Case Western Reserve University School of Medicine and Rainbow Babies and Children's Hospital, Cleveland, OH, USA

[4]Genentech, Inc., South San Francisco, CA, USA

[5]Nemours Children's Clinic, Orlando, FL, USA

SUMMARY

Objectives—We evaluated safety and efficacy of recombinant human growth hormone (rhGH) for improving growth, lean body mass (LBM), pulmonary function, and exercise tolerance in children with cystic fibrosis (CF) and growth restriction.

Study design—Multicenter, open-label, controlled clinical trial comparing outcomes in prepubertal children < 14 years with CF, randomized in a 1:1 ratio to receive daily rhGH (Nutropin AQ) or no treatment (control) for 12 months, followed by a 6-month observation (month 18). Safety was monitored at each visit, including assessments of glucose tolerance.

Results—Sixty-eight subjects were randomized (control n = 32; rhGH n = 36). Mean height standard deviation score (SDS) in the rhGH group increased by 0.5 ± 0.4 at 12 months (mean ± SD, $p < 0.001$); the control group height SDS remained unchanged. Weight increased by 3.8 ± 1.8 vs 2.8 ± 1.5 kg, (mean ± SD, $p = 0.0356$) and LBM increased by 3.8 ± 1.8 vs 2.1 ± 1.4 kg ($p = 0.0002$) in the rhGH group vs controls, respectively. Forced vital capacity increased by 325 ± 319 in the rhGH group compared with 178 ± 152 mL in controls (mean ± SD, $p = 0.032$). Forced expiratory volume in 1 second improved in both groups with a significant difference between groups after adjustment for baseline severity (LSMeans ± SE: rhGH, 224 ± 37, vs controls, 108 ± 40 mL; $p = 0.04$). There was no difference between groups in exercise tolerance (6-minute walk distance) at 1 year. Changes in glucose tolerance for the two groups were similar over the 12-

Corresponding Author: Michael S. Stalvey, MD, University of Massachusetts Medical School, Department of Pediatrics, Pediatric Endocrinology, 55 Lake Avenue North, Worcester, MA 01655, USA, Phone: 508-856-1470, Fax: 508-856-1552, Michael.Stalvey@umassmed.edu.

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month study period, with three subjects developing IGT and one CFRD in each group. One rhGH-treated patient developed increased intracranial pressure.

Conclusions—Treatment with rhGH in prepubertal children with CF was effective in promoting growth, weight, LBM, lung volume, and lung flows, and had an acceptable safety profile.

Keywords

safety; efficacy; pulmonary function; body composition; growth

INTRODUCTION

Cystic fibrosis (CF) continues to be the leading life-limiting genetic disorder in Caucasian individuals. The disease is transmitted as an autosomal recessive mutation in the CF transmembrane conductance regulator (CFTR) gene, which encodes for a chloride ion channel protein.[1,2] Although the direct impact of the CFTR mutation on growth is unclear, the overall effects of the disease on growth and body weight are prominent. Many individuals with CF do not achieve normal linear growth or predicted adult height[3] and manifest poor weight gain and reduced lean body mass (LBM).[4] In patients with CF, associations have been demonstrated between predicted survival and height[5] as well as height for age and lung function.[6] Wasting has been shown to independently predict poor survival.[7] Considering these findings, the achievement of optimal height and weight is a key therapeutic objective.

Current strategies in CF treatment to improve weight, and subsequently growth, focus on nutritional supplements and appetite stimulation. Although improvements in nutrition are credited as one of the major factors for improved survival, there are no data showing effects of enhanced nutrition on the chronic catabolic state associated with CF.[1] Furthermore, Hardin et al reported an inverse correlation between the basal rate of proteolysis and patients' clinical status scores.[8] Appetite stimulants increase intake, and potentially improve weight, but often without improvement in LBM.[9]

In healthy children undergoing spontaneous growth, LBM increases with age.[10] As children with CF age, a widening gap develops between the LBM of CF children and healthy controls.[11] Additionally, in older children, there is an increase in disease severity.[11] Since declines in LBM are associated with worsening lung function and overall health,[12–14] preserving or increasing LBM is considered a priority in CF management. Thus, treatment with recombinant human growth hormone (rhGH) in younger children, when they appear to be responsive to its anabolic effect, may be a good strategic approach.

Growth hormone (GH), delivered exogenously as rhGH, promotes anabolism and stimulates skeletal growth in pediatric patients with growth failure due to inadequate endogenous GH secretion as well as other chronic and congenital conditions.[15] Previous studies of rhGH in CF individuals demonstrated improvements in growth velocity, weight gain, indices of metabolism, and clinical status.[16–21] However, these studies had small sample sizes or short duration of therapy that warranted further investigation in a controlled clinical trial. Further,

due to concerns about precipitating CF-related diabetes, more data on rhGH-related development of glucose intolerance and diabetes were needed.

In this multicenter, randomized, open-label, controlled trial, our hypothesis was that rhGH would increase growth and LBM in prepubertal CF children with growth restriction. Further, we hypothesized that improved growth would increase lung capacity and thereby improve pulmonary function and exercise tolerance in these children without negatively impacting glucose tolerance.

METHODS

This was a phase 2, multicenter, randomized, controlled, open-label 18-month trial of the safety and efficacy of rhGH administered subcutaneously (SC) daily in prepubertal children with CF and growth restriction.

Subjects were randomized in a 1:1 ratio to either rhGH (Nutropin AQ, Genentech, Inc., South San Francisco, CA) 0.043 mg/kg/day (0.3 mg/kg/wk) or to no treatment (further identified as “controls”) for 12 months. A permuted block randomization scheme was generated by an interactive voice response system (IVRS) for group assignment at each study site. For this open-label trial, there was no allocation concealment. The rhGH dose was adjusted for weight change at each visit. After completion of Month 12, all subjects were observed for an additional 6 months (further identified as the “Month 18 visit”), with no rhGH treatment for either group.

The study was conducted according to the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) and within US requirements. Informed consent forms were signed by the subject or the subject’s legally authorized representative before his/her participation in the study. A Data Monitoring Committee (DMC) conducted periodic reviews of safety. The trial was registered on ClinicalTrials.gov.

Subject Selection

Inclusion criteria included: 1) diagnosis of CF by sweat test (chloride concentration > 60 mmol/L) or genetic testing (for mutations known to cause CF); 2) prepubertal, ages 5–12 years for girls and 5–13 years for boys; 3) height ≤ 10th percentile for age and sex; 4) bone age ≤ 10 years for girls and ≤ 11 years for boys by the method of Greulich and Pyle[22]; 5) prepubertal status defined as Tanner Stage 1; 6) ability to perform pulmonary function tests in a reproducible manner; 7) normal thyroid function; and 8) adequate caloric intake following the Cystic Fibrosis Foundation guidelines.[23] Exclusion criteria included: 1) prior or current rhGH use; 2) documented GH deficiency; 3) history of impaired glucose tolerance (IGT) or CF-related diabetes (CFRD) or evidence of IGT or CFRD in the screening glucose tolerance test; 4) infection with *Burkholderia cepacia*; 5) qualitative change in antibiotic treatment (e.g., for exacerbation of lung infection) within 14 days of study entry; 6) hospitalization or treatment with systemic corticosteroids during the 30 days prior to study; 7) inability to adhere to adequate oral nutritional regimen; 8) need for parenteral nutritional supplementation; 9) required scheduled elective hospitalizations for IV antibiotic therapy; or

10) participation in other investigational studies within 30 days of enrollment or during the study, except for participation in observational and questionnaire studies.

Assessments

Height and weight were measured every 3 months for the 12-month study and again at the Month 18 visit. Height standard deviation score (SDS) was calculated using Centers for Disease Control and Prevention (CDC) Growth Charts 2000.[24] Average height velocity during the first 12 months also was calculated. LBM was measured by whole-body dual energy x-ray absorptiometry (DEXA) scans at baseline, 6 and 12 months, and at the Month 18 visits. DEXA scans were performed using a known three-section phantom to facilitate calibration for low, medium, and high percentage fat targets, and were interpreted at a central reading center at Tufts University (Boston, MA). Tanner stage for pubertal status was assessed at each visit.

Spirometry was performed at baseline, every 3 months during the 12-month study, and at the Month 18 visit. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow during the middle half of the forced vital capacity ($FEF_{25\%–75\%}$) were recorded. Percent predicted pulmonary function test values were calculated using the Wang and Dockery equations[25] to convert absolute values for use in standardized comparisons over time for individual subjects and groups. The 6-minute walk test was performed as a clinical outcome measure of exercise tolerance at baseline, 6 and 12 months, and at the Month 18 visit, using a prespecified 100 feet or greater area in each clinic.

The insulin-like growth factor-I (IGF-I) assay was performed by Esoterix, Inc. (Calabasas, CA) using an acid/ethanol extraction method. Quest Diagnostics Inc. (Van Nuys, CA) served as the central laboratory for analyses of insulin and glucose. Casual glucose monitoring was done at each site. Anti-GH antibody assays were conducted by Genentech, Inc. (South San Francisco, CA).

Measures of glucose tolerance were obtained throughout the study to monitor for the emergence of IGT or CFRD. Oral glucose tolerance tests (OGTTs) were performed at 0 and 12 months, and Month 18 visits (standard oral glucose load of 1.75 g/kg to a maximum of 75 g; blood samples at 0 and 120 minutes for glucose concentration). Insulin sensitivity was calculated via the homeostasis model assessment of insulin resistance (HOMA-IR) using fasting insulin and fasting plasma glucose concentrations measured at 0, 6 and 12 months, and Month 18 visits. HOMA-IR was calculated as follows: [fasting insulin (mU/L) × fasting glucose (mg/dL)]/405.[26] Hyperglycemia was defined as either a fasting plasma glucose result of ≥ 126 mg/dL or a 2-hour OGTT glucose result of ≥ 140 mg/dL; IGT was defined as an OGTT 2-hour plasma glucose between 140 and 199 mg/dL; CFRD was defined as an OGTT 2-hour plasma glucose ≥ 200 mg/dL, fasting plasma glucose (FPG) result of ≥ 126 mg/dL on two or more occasions, FPG ≥ 126 mg/dL plus casual glucose level ≥ 200 mg/dL, or casual glucose levels ≥ 200 mg/dL on two or more occasions.[27]

Statistical Methods

Analyses of growth, LBM, pulmonary function, and exercise tolerance included all randomized subjects according to their assigned treatment (intent-to-treat). Safety

comparisons between groups included all subjects in the control group and all those in the rhGH group who received at least one injection of rhGH.

Changes from baseline to Month 12 in height SDS and LBM were analyzed for both differences between treatment groups and differences within treatment groups using Student's *t*-tests. A Hochberg-Bonferroni procedure was used to maintain an overall Type I error of $\alpha = 0.05$ for the co-primary outcomes.[28] All other outcomes were analyzed similarly, but without adjustment for multiplicity. Pre-specified analyses included both between- and within-group changes. Changes in LBM from baseline to Month 12 and from Month 12 to Month 18 were analyzed only for participants whose DEXA scans were performed using equipment from the same manufacturer to ensure consistency of the measurements. Pulmonary function tests were analyzed with Student's *t*-tests without adjusting for baseline imbalances as pre-specified, as well as with analysis of covariance (ANCOVA) adjusting for baseline disease severity (FEV_1 % predicted), age, and height SDS in a post hoc exploratory analysis. Serum concentrations of IGF-I were summarized at baseline, 6 and 12 months, and Month 18 visits. Missing values were not imputed. All analyses were conducted using SAS v.9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Sixty-eight subjects were randomized at 24 sites; 32 to the control group and 36 to the rhGH group. One study site was closed because of its failure to comply with the study protocol. The five subjects followed at that site were excluded from efficacy analyses, but available data were included in safety assessments. An additional subject was incorrectly randomized to the rhGH group and was immediately discontinued from the study. The remaining 62 subjects were included in the efficacy analyses. In the rhGH group, one subject discontinued as a result of an adverse event, and one subject died during the observation period prior to the Month 18 visit (as described below in safety results). Other reasons for early discontinuation included lost to follow-up and subject's decision. Of the 32 subjects randomized to the control group, 32 were included in the safety analysis, 29 were included in the efficacy analysis; 27 completed Month 12 (2 subjects decided to withdraw), 26 subjects completed Month 18 (1 additional subject was lost to follow-up). Of the 36 subjects randomized to the rhGH group, 35 were included in the safety analysis (1 was incorrectly randomized and was withdrawn prior to receiving study drug); 33 were included in the efficacy analysis, 29 completed Month 12 (1 subject discontinued due to an adverse event, 1 was lost to follow-up, and 2 subjects decided to withdraw); 27 subjects completed Month 18 (1 subject died between Months 12 and 18, and 1 additional subject decided to withdraw).

Overall, the demographics and baseline characteristics for the two groups, including IGF-I levels, were similar (Table 1). However, baseline FEV_1 and FVC were lower in the rhGH group than in the control group for both absolute and percent predicted values. Distance walked in 6 minutes at baseline was also lower in the rhGH group than in the control group. These unexpected imbalances at baseline led to the post-hoc adjusted analyses.

GROWTH

The difference between the groups in annualized height velocity (change from baseline to Month 12) was statistically significant (mean [95% CI]: 2.9 cm [2.0–3.9]; $p < 0.0001$). Annualized height velocity at Month 12 was 8.2 ± 2.1 cm/yr for the rhGH group and 5.3 ± 1.3 cm/yr for the control group. At Month 12, the mean change from baseline in height SDS was also statistically significant between the groups with the rhGH group showing a +0.5 SDS advantage ($p < 0.0001$). The within-group change for the rhGH group was statistically significant (+0.5 SDS; $p < 0.0001$), but not for the control group which showed no change (0.0 SDS, $p = 0.8904$) (Table 2, Fig. 1). From Month 12 to Month 18, the control group remained at the same mean height SDS (0.0 SDS change) while the rhGH group experienced a slight decline (−0.1 SDS change), but maintained the 0.5 SDS advantage over the control group.

Mean IGF-I levels were very similar at baseline for the two groups (rhGH group, 122.4 ± 56.9; control group, 124.0 ± 54.3), but had increased in the rhGH group at Months 6 and 12 (198.3 ± 91.2 and 210.5 ± 108.8, respectively). These levels were greater than in the control group at Months 6 and 12 (141.0 ± 51.3 and 139.5 ± 77.4, respectively). By Month 12, the mean change from baseline was 15.2 ± 60.7 ng/mL for the control group and 88.2 ± 69.7 ng/mL for the rhGH group, but the increased IGF-I levels in the rhGH group did not persist at Month 18 (off treatment) (rhGH group, 137.3 ± 92.3; control group, 160.6 ± 100.4).

BODY WEIGHT

Both groups had statistically significant weight increases ($p < 0.001$) from baseline to Month 12 (Table 2, Fig. 2). In addition, the change from baseline to Month 12 in the rhGH group (3.8 ± 1.8 kg) was significantly greater than in the control group (2.8 ± 1.5 kg) ($p = 0.0356$). Between Month 12 and Month 18, both groups continued to gain weight; however, there was no significant difference between the groups.

LEAN BODY MASS

The change in LBM from baseline to 12 months was one of the two co-primary outcomes of the study. The rhGH group had a significantly greater increase in LBM than the control group of 1.8 kg (95% CI: 0.9–2.7), $p < 0.0002$. From baseline to Month 12, both groups showed statistically significant increases in LBM; 3.8 ± 1.8 kg for the rhGH group and 2.1 ± 1.4 kg for the control group (both $p = 0.0001$) (Table 2) with all but one subject in each group gaining some LBM. One subject in the control group was excluded from the analysis of LBM due to a change in the DEXA equipment used for the scan at Month 12. During the observation period between Months 12 and 18, the control group had a gain in LBM (1.1 ± 0.9 kg, $p < 0.0001$) but the rhGH group did not change significantly.

At baseline, LBM as the mean proportion of total body composition was the same for the two study groups (78% ± 6%). By Month 12, the mean percent LBM had increased to 81 % ± 5% for the rhGH group (+3.3%; $p < 0.0001$) and 79% ± 7% for the control group (+1%, p = NS); the 2.2% difference between the groups was not statistically significant ($p = 0.0619$). By the Month 18 visit, both groups had experienced declines in LBM (rhGH group: −3.3% ± 3.4% and control group −1% ± 4.7%).

During the study some of the patients entered puberty, which can affect growth rates independent of treatment. By Month 12, nine boys (control n = 5; rhGH n = 4) and two girls (both control) were Tanner stage ≥ 2. Overall, the results for height SDS and LBM for the subgroup of subjects who were Tanner stage 1 at Month 12 were similar to those obtained for all subjects. By Month 18, 10 boys (control n = 4; rhGH n = 6) and 7 girls (control n = 5; rhGH n = 2) were Tanner stage ≥ 2, and again it did not affect the differences seen between groups.

PULMONARY FUNCTION AND EXERCISE TOLERANCE

Pulmonary function test results are summarized in Table 3. Baseline FVC, FEV_1, and $FEF_{25\%–75\%}$ were higher in the control subjects than in those randomized to receive rhGH. Without accounting for these baseline differences, subjects in both groups showed statistically significant increases from baseline in mean absolute FVC during the 12-month study treatment period ($p < 0.0001$). The difference in the mean change from baseline was also significantly higher for the rhGH group than for the control group ($p = 0.0318$). The control group continued to have a significant increase in FVC during the follow-up period from Month 12 to Month 18 ($p < 0.0001$), but the change in the rhGH group during that period was not significant ($p = 0.6353$). There were no significant changes from baseline to Month 12 for percent predicted FVC within the treatment groups, nor was there a significant difference between the groups for the change in this period (Table 3). There were also no statistically significant changes within or between groups during the off-treatment follow-up period from Month 12 to Month 18.

The results for FEV_1 were similar to those for FVC. Although the analysis unadjusted for baseline imbalances showed no statistically significant difference between the groups in the mean change from baseline to Month 12 ($p = 0.1091$), adjusting for baseline disease severity, age, and height SDS, the improvement in FEV_1 was greater for the rhGH group ($p = 0.04$) (Table 4). The results for change from Month 12 to Month 18 for FEV_1 were similar to those for FVC during the same period (Table 3). No statistically significant differences in percent predicted FEV_1 over time within each group were seen. There was no significant difference between groups for change in $FEF_{25\%–75\%}$ from baseline to Month 12 (Table 4).

PULMONARY EXACERBATIONS

Nine control subjects and 10 rhGH subjects required hospitalization for pulmonary exacerbations during the 12-month study treatment period. An additional control subject and 2 rhGH subjects required IV antibiotics without hospitalization. There was no significant difference in these exacerbation events between groups.

SIX-MINUTE WALK

The 6-minute walk test was performed as a measure of exercise tolerance at baseline and at Months 12 and 18. Baseline differences and variability were considerable between the two groups (rhGH, 491.1 ± 119.5 m; control, 519.6 ± 133.3 m; Table 1). The mean distance walked in the rhGH group increased by 50.0 ± 128.5 meters (10.3%) between baseline and Month 12 ($p = 0.0437$), The change from baseline to Month 12 for the control group showed no significant increase (24.1 ± 136.2 m [4.6%]; $p = 0.3668$). The difference between the

groups in the change from baseline in distance walked was not statistically significant (26.3 [95% CI, (−44.8, 97.4)] p= 0.4611). From Month 12 to Month 18 neither group had a statistically significant change, nor was there a significant difference between the groups. Two control and four rhGH-treated subjects were reported “not clinically stable” during one of the tests and their data were excluded. No subjects required supplemental oxygen for these visits.

GLUCOSE TOLERANCE

FPG, fasting insulin, and HOMA-IR were all very similar at screening visit for the two groups (Table 5). In the control group, there was no change from baseline values in FPG. In the rhGH group, FPG rose from a mean ± SD baseline value of 87.1 ± 9.7 mg/dL to 90.0 ± 11.8 mg/dL by Month 12 ($p < 0.05$) and returned to screening levels at Month 18. Fasting insulin concentrations (mean ± SD, uU/mL) were lower at screening than at Month 12, for both control (3.4 ± 2.5 vs. 7.4 ± 8.2) and rhGH groups (4.1 ± 3.4 vs. 7.1 ± 4.0, $p = 0.002$). These values were reduced, but still above baseline at Month 18 (controls 6.2 ± 5.3, p = NS; and rhGH 5.1 ± 2.2, $p = 0.007$). Fasting insulin concentrations were significantly lower in the rhGH-treated group, compared with the control group, at the 18-month visit (p=0.004). There were no statistically significant differences seen in HOMA-IR either within or between groups.

Episodes of hyperglycemia, as defined in Methods, had occurred in 5 (15%) of the rhGH subjects and 7 (24%) of the control subjects by Month 12 (relative risk [RR] [95% confidence interval {CI}] = 0.63 [0.22, 1.76]). Only one subject (control group) had more than one occurrence of hyperglycemia in the first 12 months. Between the 12-month and 18-month visits, an additional two control and five rhGH subjects had a first occurrence of hyperglycemia. Thus, the RR (95% CI) of having an episode of hyperglycemia for the rhGH group compared with the control group was 0.98 (0.46, 2.07) for the 18-month study period. One subject in the rhGH group had more than one occurrence by the end of Month 18. There was no increase in the risk of hyperglycemic episodes for subjects in the rhGH group compared with the control group.

Twenty-five subjects in the rhGH group and 24 subjects in the control group had normal glucose tolerance during the 18-month study period. Despite IGT as a study exclusion criterion, three subjects in the rhGH group and two subjects in the control group had IGT at screening/baseline. Two of the subjects with IGT in the rhGH group had subsequently normal OGTT results at both Month 12 and Month 18. In each study group, three subjects developed IGT and one developed CFRD during the first 12 months of the study, corresponding with the treatment period. Additionally, elevated FPG levels occurred in one rhGH subject and two control subjects. During the observation period but prior to the 18-month visit, two additional rhGH subjects developed IGT, a third subject continued to have evidence of IGT (noted at baseline), and one subject developed CFRD. In the control group, one additional subject developed IGT.

SAFETY

Almost all subjects reported at least one adverse event; 32 subjects (100%) in the control group and 34 subjects (97%) in the rhGH group. The number of subjects who experienced serious adverse events (12) was the same for both groups. Serious adverse events that occurred during the study were mostly pulmonary exacerbations and were reported equally by the two groups.

Ten subjects in the rhGH group were reported to have experienced a study drug–related adverse event: Seven subjects had injection-site reactions/bruising, five had hyperglycemia, with one of these subjects discontinuing from the study, and one had papilledema and headache after 5 months of rhGH, resulting in study discontinuation. This subject likely had a recognized rhGH-related adverse event, benign intracranial hypertension, though a lumbar puncture was not performed. The event resolved when rhGH was discontinued. One subject died of respiratory failure approximately 3 months after the Month 12 visit (the time of his last rhGH injection) and ~ 3 months prior to the Month 18 visit. The death was reported as unrelated to study drug.

DISCUSSION

Regulation of growth in CF goes beyond genetic and environmental factors. Disease-related increase in caloric needs occurs due to increased resting energy expenditure, chronic malabsorption, and protein catabolism.[2,29,30] Improving weight via nutritional means is a mainstay of CF care; however, the focus has not been on mitigating chronic catabolism. GH has major anabolic actions, including increasing LBM. Its use in pediatrics has primarily been for improving growth; in CF its anabolic actions might be beneficial in disease modification. There have been several studies of rhGH in CF,[17–19,31–33] but the current study focused on short prepubertal children, who are likely to have greater need for augmentation of growth, but have not been systematically studied as a group.

Our 12-month treatment trial demonstrated that treatment with rhGH effectively increased height SDS, lean body mass, and body weight in prepubertal children with CF compared with control CF subjects. Body composition data demonstrated that achievements in weight gain were primarily in the form of LBM for the rhGH-treated group. The recent Phung systematic review and meta-analysis included our preliminary data (taken from poster and abstract presentations) on improvements in height, weight, and LBM. Those data were similar to the composite data from the other nine controlled and eight observational studies of rhGH in CF included in their analysis.[21] Our reported improvements in growth and weight did not persist beyond the 12-month treatment period. The decline in height velocity is consistent with the catch-down growth described following discontinuation of rhGH in growing children.[34,35] It is unclear if the lack of maintenance of the weight gain was secondary to attenuated growth or the absence of a potential direct effect of rhGH on food intake.[36]

Growth status and pulmonary health in CF are closely linked, with population-based studies showing that normal height and weight are associated with better pulmonary function and less morbidity and mortality.[37] Studies that followed growth and lung function parameters

longitudinally demonstrated that reduced growth and nutrition measures predicted lower pulmonary function later, but those who were able to improve or maintain steady growth and weight gain had better pulmonary function outcomes.[6,38,39] These studies support the hypothesis that aggressive nutrition and growth interventions early in life may optimize lung health and survival. In fact, better linear growth may be associated with better lung growth (higher lung volumes) and better lung function, independent of the beneficial effect of weight gain.[21]

In this study, the randomization schedule did not include stratification for pulmonary function, resulting in an imbalance between the groups at baseline. Nevertheless, the children treated with rhGH for 12 months had a significantly larger gain than the control group in absolute FVC and, after correcting for baseline disease stage, age, and height, the absolute FEV_1 was also significantly improved in the treated group. There were no significant changes in the percent-predicted values, however, demonstrating that lung function increased in proportion to somatic growth in the treated children. Our findings are in line with the recent review of rhGH in CF, which also revealed that a longer duration of treatment is more likely to demonstrate improvement in lung function than shorter periods (i.e.,12 vs 6 months).[21] We can only speculate whether the increase in lung volume confers a survival effect; this would require much longer study duration to determine.

In this study, there was no difference noted between groups in the change in exercise tolerance as measured by the six-minute walk test. It is likely that this test is too blunt an instrument to use for this purpose. While the test was chosen due to its simplicity and low cost, there are many factors that increase the variability of the results, including subject motivation, height, and physical and cardiopulmonary fitness. The test is more sensitive in patients with moderate to severe lung disease, and there is a lack of longitudinal reference values in children. More sophisticated tests like cycle ergometry may be necessary to distinguish between treatment groups.[19]

Exacerbations of pulmonary disease are often treated with intravenous antibiotics and hospitalization, which represents a large cost and treatment burden. A recent review showed that rhGH treatment may reduce the need for these interventions,[21] but our study showed no difference in pulmonary exacerbations between the treated and control groups. In our study only one-third of the subjects required hospitalization, far lower than the rate of hospitalization in the review. This may either indicate that our subjects were healthier at baseline or that the criteria for when to hospitalize for a pulmonary exacerbation differed among centers. In either case it would take a much larger trial with more uniform criteria to determine a treatment benefit for this outcome.

A major concern for use of rhGH in CF is the potential to induce insulin resistance[40] and lead to or exacerbate diabetes. CFRD is a leading comorbidity associated with CF (incidence of 21.5%).[2,41] Previous studies in the use of rhGH in CF did not demonstrate a precipitation of diabetes.[19,33] In their systematic review, Phung et al reported variable glucose responses to rhGH therapy in CF. Although no significant increases in glucose intolerance were described, a minimal but significant increase in fasting glucose was reported.[21] Nevertheless, a recent report in pediatric and adult CF patients suggests that impaired fasting

glucose alone is not deleterious, may not lead to further glucose deterioration, and could be associated with improved survival.[42] A major endpoint of our study was the impact of rhGH treatment on glucose tolerance and insulin sensitivity. There were no statistically significant differences in glucose abnormalities (FPG, fasting insulin, and HOMA-IR) between the rhGH and control groups in the first 12 months of the study. Following rhGH cessation, at the 18-month visit, there was a suggestion of increased glycemic abnormalities in previously rhGH-treated subjects. Because glycemic abnormalities develop in the natural course of CF, and given the small study size, we cannot assess whether increased abnormalities during the observation period were related to the previous rhGH therapy.

One weakness of our research study was the open-label design of the protocol. However, given the injectable nature of the drug delivery, a placebo injection protocol design was not considered acceptable. A second weakness was the lack of stratification of the groups for disease stage (PFT values). This resulted in an imbalance between the groups at baseline, with reduced FEV_1 and FVC values in the rhGH group and small differences in the baseline results of the 6-minute walk test. The difference at baseline between groups may have obscured even greater gains in pulmonary function values in the rhGH group.

In summary, treatment with rhGH in prepubertal children with CF was efficacious in promotion of growth, weight, and LBM. Additionally, we noted an improvement in absolute FEV_1 and FVC, but not FEV_1 percent predicted or FVC percent predicted. These effects were obtained without producing significant evidence of glucose intolerance or insulin resistance. Benign intracranial hypertension occurred in one subject, which merits careful monitoring in patients treated with rhGH. Longer-term studies are required to determine whether increased somatic growth rate and improvements in LBM result in improved lung function and improved survival.

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ABBREVIATIONS

CF	Cystic fibrosis
CFRD	Cystic fibrosis–related diabetes mellitus
CFTR	Cystic fibrosis transmembrane conductance regulator
DEXA	Dual-energy x-ray absorptiometry
$FEF_{25\%–75\%}$	Forced expiratory flow during the middle half of the forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FPG	Fasting plasma glucose
FVC	Forced vital capacity
GH	Growth hormone
HOMA-IR	Homeostasis model assessment of insulin resistance
IGF-I	Insulin-like growth factor I
IGT	Impaired glucose tolerance
LBM	Lean body mass
OGTT	Oral glucose tolerance test
rhGH	Recombinant human growth hormone
SDS	Standard deviation score

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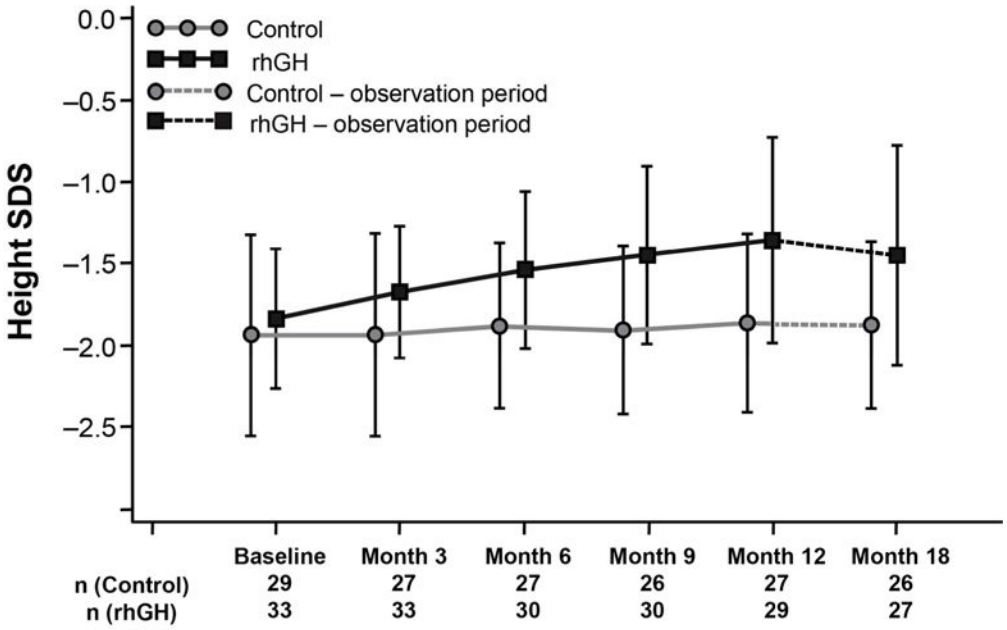

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Figure 1.

Height Standard Deviation Score (SDS) by visit (as randomized subjects), measured in pre-pubertal CF children at each study visit, for the rhGH study group and control group. There was no significant increase in the height SDS of the control group from baseline to the 12-month visit (Hochberg-adjusted $p = 0.8904$). The rhGH group demonstrated a significant increase in height SDS from baseline to the 12-month visit (Hochberg-adjusted $p < 0.0001$). Additionally, the change from baseline to the 12-month visit was significantly greater for rhGH-treated subjects compared with the control subjects ($p < 0.001$). Hochberg-adjusted p values for changes from Month 12 to Month 18: Control $p = 0.7007$ and rhGH $p = -0.0027$. Error bars represent standard deviations.

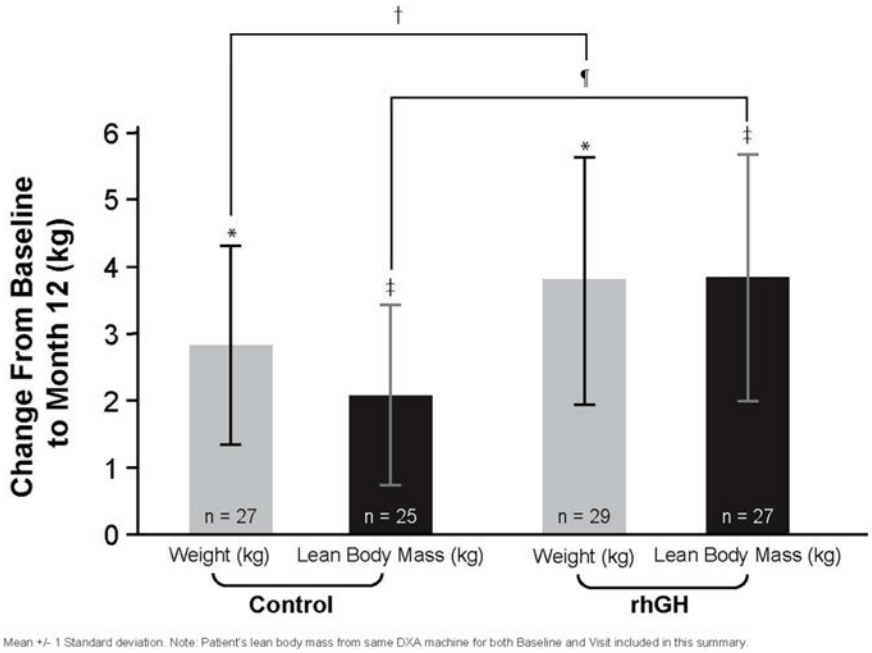

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Figure 2.

Weight and lean body mass (LBM) change from baseline to Month 12 (as randomized subjects) in pre-pubertal CF children. LBM was compared from subjects measured on the same DXA machines for both baseline and Month 12 visit. Values expressed as mean ± 1 standard deviation. Weight increased in both the control group and the rhGH group between baseline and Month-12 visits (*$p < 0.001$ for both). However, weight increase from baseline was significantly greater for the rhGH group compared with the control group ($^{\dagger}p = 0.0356$). LBM increased in both the control and rhGH study groups from baseline to Month 12 visit ($^{\ddagger}p = 0.0002$ for both). Additionally, the increase in LBM for the rhGH group was greater than for the control group ($^{\P}p < 0.0001$).

TABLE 1

Baseline Characteristics: Randomized Subjects

Baseline Characteristic	Control (n = 29, 62% male) Mean (SD), range	rhGH (n = 33, 66.7% male) Mean (SD), range
Chronologic age, yr	9.4 (2.2.), 5.4 to 13.2	9.4 (2.0), 5.2 to 13.4
Bone age, yr	7.8 (2.2), 3.0 to 11.5	7.7 (2.0), 3.5 to 11.5
Weight, kg	24.8 (5.8), 15.8 to 38.6	24.2 (5.0), 14.7 to 35.1
Height, cm	123.2 (11.8), 104.5 to 144.6	123.3 (10.2), 100.4 to 143.8
Height SDS	−1.9 (0.6), −3.5 to −1.2	−1.8 (0.4), −2.9 to −1.2
Total lean body mass, kg	19.1 (4.0), 12.3 to 28.0	18.4 (3.9), 11.7 to 26.5
6-minute walk distance, m	519.6 (133.3), 228.0 to 747.0	491.1 (119.5), 251.0 to 731.0
IGF-I, ng/mL	124.0 (54.3), 35.0 to 254.0	122.4 (56.9), 38.0 to 286
Pulmonary Function		
FEV_1, mL	1400.3 (495.3), 660.0 to 2620.0	1209.1 (450.5), 310.0 to 2620.0
FEV_1 % predicted	94.6 (18.5), 52.8 to 128.5	81.9 (24.5), 28.6 to 125.2
FVC, mL	1692.4 (595.9), 700.0 to 3230.0	1555.8 (456.7), 860.0 to 2950.0
FVC % predicted	102.2 (18.6), 54.6 to 146.6	94.2 (18.2), 57.3 to 125.4

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IGF-I, insulin-like growth factor-I; rhGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score

TABLE 2

Height SDS, Lean Body Mass, and Body Weight: Randomized Subjects

Outcome and Timepoint	Control (n = 29) Mean (SD), range	rhGH (n = 33) Mean (SD), range
Height SDS		
At baseline	−1.9 (0.6), −3.5 to −1.2	−1.8 (0.4), −2.9 to −1.2
At Month 12	−1.9 (0.5), −3.1 to −0.9	−1.4 (0.6), −3.6 to −0.2
At Month 18	−1.9 (0.5), −3.0 to −1.1	−1.4 (0.7), −3.9 to −0.3
Change from baseline to Month 12	−0.0 (0.2)[1], −0.5 to 0.6	0.5 (0.4)[2,3], −0.6 to 1.1
Change from Month 12 to Month 18	−0.0 (0.1)[4], −0.3 to 0.2	−0.1 (0.2)[5,6], −0.4 to 0.3
Lean body mass, kg		
At baseline	19.1 (4.0), 12.3 to 28.0	18.4 (3.9), 11.7 to 26.5
At Month 12	21.5 (4.6), 13.5 to 31.9	22.2 (4.9), 15.4 to 32.1
At Month 18	22.2 (5.0), 13.8 to 35.3	22.2 (4.9), 13.9 to 32.2
Change from baseline to Month 12	2.1 (1.4)[7], −2.3 to 4.0	3.8 (1.8)[7,3], −0.6 to 6.7
Change from Month 12 to Month 18	1.1 (0.9)[8], −0.1 to 3.3	−0.3 (1.4)[4,6], −3.1 to 3.1
Weight, kg		
At Baseline	24.8 (5.8), 15.8 to 38.6	24.2 (5.0), 14.7 to 35.1
At Month 12	27.6 (6.4), 17.0 to 40.3	27.8 (5.5), 17.6 to 38.1
At Month 18	28.7 (6.8), 18.3 to 43.9	29.1 (6.1), 18.0 to 41.3
Change from baseline to Month 12	2.8 (1.5)[9], 0.0 to 6.9	3.8 (1.8)[9,10], −2.1 to 7.3
Change from Month 12 to Month 18	1.4 (1.6), −0.9 to 4.6	1.0 (1.2)[11], −2.8 to 3.2

SD, standard déviation; SDS, standard deviation score

[1] Change from baseline was not statistically significant.

[2] Change from baseline showed significant increase with $p < 0.0001$.

[3] Change from baseline to 12-month visit was significantly greater in the rhGH group than in the Control group, $p < 0.0001$

[4] Change from 12-month visit to 18-month visit was not significant.

[5] Change from 12-month visit to 18-month visit showed significant decrease, with $p < 0.001$.

[6] Change from 12-month visit to 18-month visit was significantly less in the rhGH group than in the Control group, $p < 0.05$

[7] Change from baseline showed significant increase, with $p = 0.0002$.

[8] Change from 12-month visit to 18-month visit showed significant increase, with $p < 0.0001$

[9] Change from baseline was significantly increased, with $p < 0.001$.

[10] Change from baseline to 12-month visit was significantly greater in the rhGH group than in the Control group, $p = 0.0356$

[11] Change from 12-month visit to 18-month visit was not significantly different between groups.

Note: Change in lean body mass (LBM) is the difference between the Month 12 LBM and baseline LBM, for subjects with baseline and Month 12 LBM from dual energy x-ray absorptiometry scans taken on machines from the same manufacturer.

TABLE 3

Pulmonary Function Tests

	Control Group			rhGH-Treated Group		
	Baseline (n = 29)	**Month 12 (n = 27)**	**Month 18 (n = 26)**	**Baseline (n = 33)**	**Month 12 (n = 29)**	**Month 18 (n = 27)**
FVC, ML	1692 ± 596	1864 ± 601	2035 ± 625	1556 ± 457	1853 ± 669[1]	1908 ± 614[2]
FEV_1, ML	1400 ± 495	1542 ± 510	1674 ± 510	1209 ± 451	1434 ± 539	1467 ± 568[2]
$FEF_{25\%–75\%}$, mL/sec	1585 ± 645	1704 ± 804	1907 ± 813	1212 ± 723	1428 ± 792	1382 ± 848[2]
FVC % predicted	102 ± 19	101 ± 16	105 ± 14	94 ± 18	95 ± 24	94 ± 23
FEV_1 % predicted	95 ± 19	94 ± 18	97 ± 15	82 ± 25	83 ± 26	81 ± 27
$FEF_{25\%–75\%}$ % predicted	68 ± 44	78 ± 38	86 ± 34	54 ± 44	57 ± 41	50 ± 41[2]
FEV_1/FVC	0.83 ± 0.08	0.83 ± 0.08	0.83 ± 0.07	0.77 ± 0.13	0.77 ± 0.11	0.75 ± 0.11

Values represented as means ± SD; $FEF_{25\%–75\%}$, forced expiratory flow during the middle half of the forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; rhGH, recombinant human growth hormone. Differences in n values reflect the subjects completing the Month-12 and 18 visits.

[1] Unadjusted change from baseline to Month 12 significantly greater in the rhGH-treated group than in the control group in FVC ($p < 0.05$).

[2] Unadjusted change from Month 12 to Month 18 significantly greater in the control group than in the rhGH-treated group in FEV_1 ($p < 0.05$), FVC ($p < 0.01$), $FEF_{25\%–75\%}$, and $FEF_{25\%–75\%}$ % predicted.

TABLE 4

Difference in Changes from Baseline to Month 12 in Pulmonary Function Tests Adjusted for Baseline Severity, Age, and Height SDS

	Difference in Adjusted Mean Changes: rhGH-Treated Group (n = 29) vs Control Group (n = 27) (LS mean ± SE)	95% Confidence Interval	p Value
FVC, ML	205 ± 65	75, 335	0.0026
FEV_1, mL	115 ± 55	5, 226	0.0406
$FEF_{25\%–75\%}$, mL/sec	61 ± 133	−208, 329	0.6517
FEV_1/FVC	−0.02 ± 0.02	−0.07, 0.03	0.3583

$FEF_{25\%–75\%}$, forced expiratory flow during the middle half of the forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LS, least squares; rhGH, recombinant human growth hormone; SE, standard error.
The n value represents subjects completing the Month-12 visit.

TABLE 5

Glucose Homeostasis: FPG, Fasting Insulin, and HOMA-IR (Mean ± SD)

	Control Group			rhGH-Treated Group		
Visit (n)	**Screening (n = 27)**	**Month 12 (n = 27)**	**Month 18 (n = 25)**	**Screening (n = 35)**	**Month 12 (n = 27)**	**Month 18 (n = 23)**
FPG, mg/mL	87.2 ± 8.3	88.9 ± 13.3	92.1 ± 9.8	87.1 ± 9.7	90.0 ± 11.8[1]	87.3 ± 8.2[2]
Fasting insulin, μU/mL	3.4 ± 2.5	7.4 ± 8.2[3]	6.2 ± 5.3	4.1 ± 3.4	7.1 ± 4.0[4]	5.1 ± 2.2[5,6]
HOMA-IR	0.7 ± 0.6	1.8 ± 2.6	1.4 ± 1.2	0.9 ± 0.8	1.0 ± 0.3	1.1 ± 0.5

FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; rhGH, recombinant human growth hormone; SD, standard deviation.
Differences in the n value is consistent with subjects at screening, versus those in which fasting blood sugar and insulin levels were obtained at the 12- and 18-month visits.

[1] Change from the screening to Month-12 visit was significantly increased, with p = 0.047.

[2] Change from the Month-12 to Month-18 visit was significantly decreased, p = 0.034.

[3] Change from the screening to Month-12 visit was significantly increased, with p = 0.016.

[4] Change from the screening to Month-12 visit was significantly increased, with p = 0.002.

[5] Change from the Month-12 to Month-18 visit was significantly decreased, p = 0.007.

[6] Fasting insulin concentrations were significantly greater in control subjects versus rhGH subjects, p = 0.004.