Recombinant Human Growth Hormone in the Treatment of Patients With Cystic Fibrosis

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KEY WORDS

cystic fibrosis, recombinant human growth hormone, systematic review, meta-analysis

ABBREVIATIONS

CF—cystic fibrosis
IBW—ideal body weight
rhGH—recombinant human growth hormone
HRQoL—health-related quality of life
FVC—forced vital capacity
FEV_1—forced expiratory volume in 1 second
BMC—bone mineral content
A1c—glycosylated hemoglobin A1c
LBM—lean body mass

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abstract

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CONTEXT: Recombinant human growth hormone (rhGH) improves growth in patients with growth hormone deficiency or idiopathic short stature. Its role in patients with cystic fibrosis (CF) is unclear.

OBJECTIVE: To review the effectiveness of rhGH in the treatment of patients with CF.

METHODS: Medline and the Cochrane Central Register of Controlled Trials were searched from the earliest date through April 2010. Randomized controlled trials, observational studies, systematic reviews/meta-analyses, or case reports were included if rhGH therapy was administered to patients with CF and data on prespecified harms, intermediate outcomes, or final health outcomes were reported. When applicable, end points were pooled by using a random-effects model. The overall body of evidence was graded for each outcome as insufficient, low, moderate, or high.

RESULTS: Ten unique controlled trials ($n = 312$) and 8 observational studies ($n = 58$) were included. On quantitative synthesis of controlled trials, several markers of pulmonary function, anthropometrics, and bone mineralization were significantly improved versus control. Results of single-arm observational studies for the aforementioned outcomes were generally supportive of findings in clinical trials. There is insufficient evidence to determine the effect of rhGH on intravenous antibiotic use during therapy, pulmonary exacerbations, health-related quality-of-life, bone consequences, or total mortality, but moderate evidence suggests that rhGH therapy reduces the rate of hospitalization versus control.

CONCLUSIONS: rhGH improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF. Improvements in bone mineral content are also promising. However, with the exception of hospitalizations, the benefits on final health outcomes cannot be directly determined at this time. *Pediatrics* 2010;126: e1211–e1226

Cystic fibrosis (CF) is a life-shortening, childhood-onset genetic disease that affects ~30 000 people in the United States.[1,2] The gene responsible for CF encodes the CF transmembrane regulator protein, which regulates sodium and chloride transport across epithelial membranes. This affects nearly all exocrine glands and produces abnormally viscous mucus and excessive secretions. The dominant clinical features are chronic lung disease and pancreatic insufficiency with poor nutrition and growth.[3,4]

Treatment advances in CF over the past 25 years have improved measures of nutrition, pulmonary function, and mortality. The median age of survival has improved consistently from 1955 to the most recent data in 2008.[2]

Growth and nutritional indices (weight for age, height for age, and percent ideal body weight [IBW]) may be predictive of future pulmonary function in children with CF. It has been suggested that improvement of linear growth in children with CF may allow more lung mass and better pulmonary function independent of improved weight gain. Poor weight and shorter height have each been shown to be independently associated with increased morbidity and mortality in patients with CF in some studies.[5–9]

Recombinant human growth hormone (rhGH) is an anabolic agent with a wide variety of actions. Some of the indications for which it is approved by the US Food and Drug Administration include the treatment of growth hormone deficiency, idiopathic short stature, Turner syndrome, Prader-Willi syndrome, and chronic renal insufficiency and for children who are small for gestational age.[10] It has been investigated for the treatment of patients with CF because of their decreased growth measures and increased energy expenditures. We aimed to review the effectiveness of rhGH in patients with CF on various intermediate and final health outcomes.

METHODS

We developed and followed a standard protocol for all steps of this review. A technical report that details methods, including literature search strategies and analysis plans, and includes evidence tables is available at www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=391.

Key Questions

We refined key questions on the effectiveness of rhGH in patients with CF and obtained input from a key informant panel that included a pediatric endocrinologist, pediatric pulmonologist, pediatric pharmacist, nutritionist, and a managed care organization representative (see "Acknowledgments"). The following key questions were formulated.

1. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes including pulmonary function, growth, exercise tolerance, and bone mineralization compared with usual care alone?
2. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes including frequency of required intravenous antibiotic treatments, frequency of hospitalization, quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality compared with usual care alone?
3. In patients with CF, what is the frequency of nonmalignant serious adverse effects that result from treatment with rhGH?
4. In patients with CF, how are efficacy, effectiveness, safety, and adverse events affected by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?
5. In patients with CF, how do the efficacy, effectiveness, safety, and adverse events of treatment with rhGH differ between subgroups of patients?

Data Sources and Searches

Two independent investigators conducted systematic literature searches of Medline (starting from 1950), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from the earliest possible date through April 2010 to identify trials and studies that explicitly evaluated the impact of rhGH on outcomes in patients with CF. A manual search of references from reports of clinical trials or review articles was conducted. We contacted authors of controlled studies to obtain information on end points not reported in the published articles, and we received a response from 1 of them.

Study Selection

Two independent reviewers assessed studies for inclusion. Studies were included if (1) they were studies of rhGH therapy, (2) they were conducted on patients with CF, (3) data on prespecified clinical or humanistic outcomes were reported, and (4) they were reports of new discovery (specifically, randomized controlled trials, observational trials, systematic reviews/meta-analyses, or case reports).

Data Extraction and Quality Assessment

Through the use of a standardized data-abstraction tool, 2 reviewers independently collected data, and disagreement was resolved through discussion. The following information was obtained from each trial when applicable: author identification; year of

publication; source of study funding; study-design characteristics and methodologic quality criteria; study population; patient baseline characteristics; comorbidities; and use of concurrent standard medical therapies. End points included pulmonary function, anthropometrics, exercise tolerance, intravenous antibiotic use, hospitalizations, health-related quality of life (HRQoL), bone mineralization, bone fracture or development of osteoporosis/osteopenia, mortality, glucose measures, and development of diabetes or malignancy.

Validity assessment was performed by using the recommendations in the *Evidence-Based Practice Center Methods Guide*.[11] Each study was assessed for the following individual criteria: comparable study groups at baseline; detailed description of study outcomes; blinding of subjects; blinding of outcome assessors; intent-to-treat analysis; description of participant withdrawals; and potential conflict of interest. In addition, randomized controlled trials were assessed for randomization technique and allocation concealment. Observational studies were assessed for sample size, participant-selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies were then given an overall score of good, fair, or poor. This rating system does not assess the comparative validity across different types of study design. For example, a "fair" controlled trial is not judged to have the same methodologic criteria as a "fair" single-arm observational study. Both study design and quality rating should be considered when interpreting a study.

We used the Evidence-Based Practice Center methodology for grading, which is based on the criteria and methods of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to assess the strength of evidence. This system uses 4 required domains: risk of bias; consistency; directness; and precision.[11] All assessments were made by 2 investigators, and disagreements were resolved through discussion. The evidence pertaining to each key question was classified into 1 of 4 broad categories ("high," "moderate," "low," or "insufficient") that describe the degree of confidence that the evidence reflects the true effect and the potential for further research to change the confidence in the estimate of effect.[11]

Data Synthesis and Analysis

When sufficient data were available, outcomes were meta-analyzed. Randomized controlled trials and prospective cohort studies were pooled together when trials compared an rhGH group to a control group, henceforth described as controlled trials. Single-arm observational studies were described qualitatively in all cases.

When pooling continuous end points, a weighted mean difference was calculated by using a DerSimonian and Laird random-effects model. In cases for which mean change scores from baseline for each group were not reported, we calculated the difference between the mean baseline and mean follow-up scores for each group. SDs of the change scores were calculated by using the method proposed by Follman et al.[13] In the event that there was more than 1 treatment group versus control, each treatment group was treated as a separate trial for meta-analysis by dividing the control group equally between the treatment groups. For dichotomous end points, weighted averages were reported as relative risks with associated 95% confidence intervals and pooled by using a DerSimonian and Laird random-effects model.

Statistical heterogeneity was evaluated by using the I^2 statistic, which assesses the degree of inconsistency not due to chance across studies and ranges from 0% to 100%; values of 25%, 50%, and 75% represent low, medium, and high statistical heterogeneity, respectively. Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for the presence of publication bias.

Statistics were calculated by using StatsDirect 2.4.6 statistical software (StatsDirect Ltd, Cheshire, England). A P value of $<.05$ was considered statistically significant for all analyses.

RESULTS

Study Identification and Characteristics

After conducting the literature search to identify articles in which the use of rhGH in populations with CF were evaluated, we retrieved 46 unique citations, and another citation was identified from other sources (Fig 1). Eighteen articles were excluded during the title and abstract review, and 2 articles were excluded during the full-text review. A total of 26 articles matched our inclusion criteria (Tables 1 and 2).

Controlled Trials

Eighteen publications of controlled trials, which represent 10 unique trials ($n = 312$), met our inclusion criteria.[3,14–38] Of the 10 trials, 8 trials compared rhGH to no treatment,[14–17,23–26] 1 trial used a placebo control,[3] and 1 trial compared rhGH alone to either glutamine or the combination of glutamine and rhGH.[20] A crossover design was used in 2 trials,[16,20] whereas the others used a parallel study design.[3,14,15,17,23–26] Only 1 trial was double-blinded.[3] Four trials received funding from foundations or government,[14–16,26] 8 trials received funding from indus-

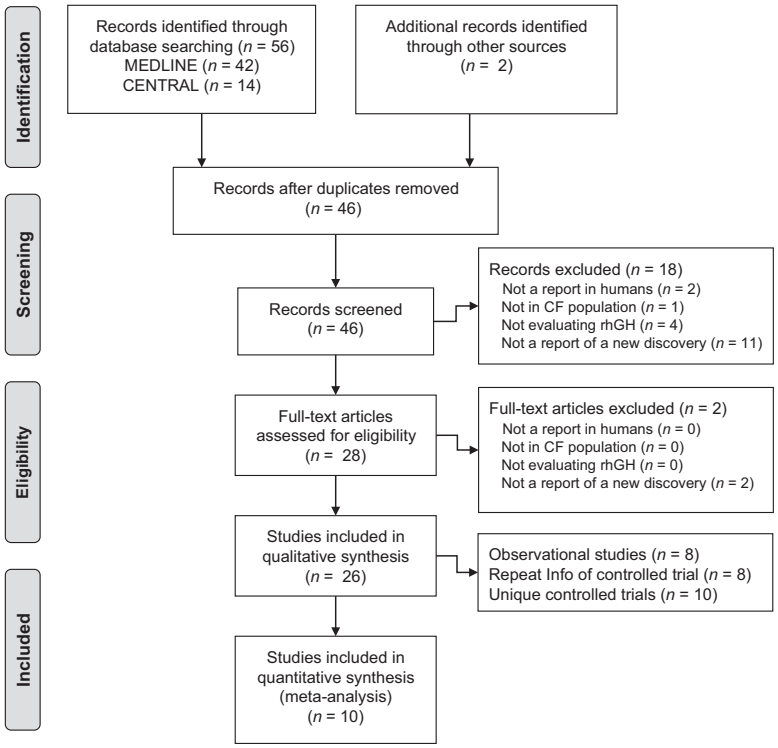

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of identification, exclusion, and inclusion of studies that evaluated rhGH therapy in patients with CF.

try,[3,14,15,17,20,23,25,26] and a funding source was not reported for 2 of the trials.[24,30] Four of the aforementioned trials received both industry and foundation funding to conduct their studies.[14–16,20,23]

In 1 of the 10 trials patients were treated with rhGH for 4 weeks,[20] whereas in the other trials patients were treated for 6 months to 1 year.[3,14–17,23–26] Chronological age of the patients was up to 23 years, but 6 trials specifically evaluated prepubertal children,[14–16,20,23–26] and 1 study evaluated only pubertal adolescents.[24] Doses of rhGH ranged from 0.23 to 0.49 mg/kg per week, and the typical dose was 0.3 mg/kg per week.[14,15,23–26] One trial evaluated 2 doses of rhGH compared with placebo.[3] Males constituted at least half of the patients in the trials, ranging from 50% to 83% of the total number of subjects.

Single-Arm Observational Studies

Eight single-arm observational reports ($n = 58$) evaluated the use of rhGH in patients with CF. Three were case reports,[31,37,38] of which 1 was of a patient with growth hormone deficiency and short stature,[31] 1 was of a patient who had previously undergone lung transplantation,[37] and another was of 2 patients with CF-related liver dysfunction.[38] One study was funded by a foundation grant,[31] 4 studies were funded by industry,[32–34,36] and 3 did not report their sources of funding.[35,37,38]

The duration of treatment with rhGH ranged from 6 months to 3 years. Ages of the patients in the studies ranged from 6 months to 13 years,[31–36,38] with the exception of 1 case report of a patient aged 18 years.[37] Doses of rhGH in the studies ranged from 0.16 to 0.35 mg/kg per week,[32,33,35,36,38] with the exception of 1 case report in which the dose was 2.2 mg/day.[37] Two studies did not report the dose of rhGH.[31,34] Baseline measures of height and weight were inconsistently reported among the observational studies, but all patients had deficient height and weight for their age.[31–38]

Data Synthesis

A summary of the results for all key questions of both qualitative and quantitative synthesis and strength of evidence is listed in Table 3. Forest plots of pooled analyses are available at www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports?pageaction=displayproduct&productid=391.

Key Question 1

Five markers of pulmonary function were evaluated in patients with CF who were receiving rhGH therapy. In controlled trials, the forced vital capacity (FVC) and percent predicted FVC significantly increased from baseline in trials that compared patients with CF who were receiving chronic rhGH therapy to control therapy. Results of single-arm observational studies support these findings. In controlled trials, the forced expiratory volume in 1 second (FEV_1) significantly increased from baseline in patients with CF who received chronic rhGH therapy versus control therapy, and the percent predicted FEV_1 showed no effect versus control. Results of single-arm observational studies support the FEV_1 findings, but the percent predicted FEV_1 findings have been mixed. In the 1 available controlled trial, no change in FEV_1 *z* score occurred in patients who received rhGH for CF versus placebo therapy, and no observational studies evaluated this parameter.

In controlled trials suitable for pooling, significant improvements in height were observed for patients with CF who received rhGH therapy versus

TABLE 1 Study Design and Population of Controlled Trials That Evaluated rhGH

Study	Study Design	Country	Study Funding	Quality Rating	Product	Dose	Follow-up Time	Inclusion Criteria	Exclusion Criteria
Hardin et al[14,15] (2001)	RCT	United States	Government, industry	Fair	Nutropin AQ	0.3 mg/kg per wk given daily	1 y	Any child who was ≤10th percentile for both height and weight, Tanner stage 1, and evaluated by nutritional staff and reported to have adequate caloric intake on at least 2 evaluations	History of glucose intolerance or previous diagnosis of CF-related diabetes; infection with *Burkholderia cepacia*; weight loss >3% during the 3 mo before study; hospitalization within 6 wk before the first study visit; treatment with systemic or oral steroids within 6 wk of the study; or questionable adherence to previous dietary recommendations designed to provide adequate nutrition
Hutler et al[16] (2002)	RCT	Germany	Foundation, industry	Fair	Genotropin	0.27–0.35 mg/kg per wk given daily	6 mo	CF confirmed by positive sweat-test result	Not specified
Schibler et al[17] (2003)	RCT	Switzerland	Industry	Fair	Saizen	0.3 mg/kg per wk given daily	1 y	CF confirmed by positive sweat-test result and analysis of mutated *CFTR* gene	Insulin-dependent diabetes mellitus, hepatic disease, evidence of portal hypertension, and clinically evident congestive heart failure
Darmaun et al[20] (2004)	RCT	United States	Foundation, industry	Fair	Not specified	0.3 mg/kg per wk given daily	1 mo	CF confirmed by positive sweat-test result and analysis of mutated *CFTR* gene; age between 7 and 13 y; Tanner stage 1; significant growth delay (as defined by height <5th percentile or below −2 SDs for age) and/or undernutrition (weight for height < 50th percentile); stable lung disease over the last 3 mo, defined as unchanged pulmonary-function test results; documented growth rate over the previous 2 y	Clinically significant liver disease (bilirubin concentration outside of normal limits and/or serum glutamine-pyruvate transaminase or serum glutamine-oxaloacetate transaminase level over twice the upper limit of normal); diabetes; or other organic disease
Hardin et al[23] (2005)	RCT	United States	Government, foundation, industry	Fair	Nutropin AQ	0.3 mg/kg per wk given daily	1 y	Prepubertal children with CF	Not specified
Hardin et al[24] (2005)	Retrospective cohort	United States	Not specified	Fair	Nutropin AQ	0.3–0.35 mg/kg per wk given daily	1 y	Adolescents referred to pediatric endocrinologist for clinical evaluation of poor growth during years 1999–2003; referral criteria: height < 5th percentile for age despite "good" nutrition and Tanner stage 3 sexual maturity	Reasons patients not referred were secondary to medical instability (frequent pulmonary infections, rapid weight loss, and systemic corticosteroid use)

TABLE 1 Continued

Study	Study Design	Country	Study Funding	Quality Rating	Product	Dose	Follow-up Time	Inclusion Criteria	Exclusion Criteria
Hardin et al[25] (2005)	RCT	United States	Industry	Fair	Nutropin AQ	0.3 mg/kg per wk given daily	1 y	Height and weight < 10th percentile for age; Tanner stage 1; enteral nutritional supplementation for at least 2 y before study enrollment; and adherence to nutritional therapy, as assessed by repeated dietary evaluation	Treatment with sustained systemic corticosteroid therapy within 6 wk of study and colonization with Burkholderia cepacia
Hardin et al[26] (2006)	RCT	United States	Industry	Fair	Nutropin AQ	0.3 mg/kg per wk given daily	1 y	Age 7–12 y; height and weight in the 25th percentile or lower for age; Tanner I breast in girls; and testicular development 3 mL or less in boys	Preexisting diabetes; systemic corticosteroid use within 6 mo; colonization with *B cepacia*; and/or addition of oral, enteral, or parenteral caloric supplements within the previous year
Schnabel et al[3] (2007)	RCT	Germany	Industry	Good	Genotropin	0.07 or 0.039 mg/kg per d (equals 0.49 or 0.273 mg/kg per wk, respectively)	6 mo	CF confirmed by positive sweat-test result and analysis of mutated *CFTR* gene; bone age 8–18 y; dystrophy defined as BMI < 10th percentile and/or body weight < 3rd percentile despite high caloric intake (>120% of the recommended dietary allowance) according to a 3-d food-intake diary	Acute pulmonary exacerbation in the 4 wk before entering the trial; diabetes (fasting plasma glucose level > 126 mg/dL); liver cirrhosis with hypoalbuminemia; serum creatinine > 120 μmol/L; inability to perform exercise and lung-function testing; history of malignancy; suspected noncompliance; participation in any other clinical trial during the active treatment phase; pregnancy or lactation; and treatment with growth hormone, anabolic steroids, or systemic corticosteroids within 12 mo
Stalvey et al[29] (2007)	RCT	United States	NR	Fair	NR	0.3 mg/kg per wk given daily	1 y	Prepubertal children with CF and height at ≤10th percentile	NR

RCT indicates randomized controlled trial; CFTR, cystic fibrosis transmembrane regulator; NR, not reported.

TABLE 2 Study Design and Population of Single-Arm Observational Studies That Evaluated rhGH

Study	Study Design	Quality Rating	Product and Dose	Duration of Treatment	Population	Reported Results
Mullis et al[31] (1991) ($N = 1$)	Case report	Poor	Grorm, dose NR	8 mo	9-y-old girl with CF and classic presentation of growth hormone deficiency, delayed psychomotor development, and extremely short stature	Improved height velocity and height *z* score for 2 mo followed by complete growth arrest, which was probably caused by anti-human growth hormone antibodies
Sackey et al[32] (1995) ($N = 7$)	Prospective; single group, all receiving rhGH	Fair	Humatrope, 0.16 mg/kg per wk given daily	6 mo in 3 patients; 12 mo in 4 patients	Prepubertal patients with CF, aged >3 y, with a height velocity at <75th percentile, and with normal serum thyroxin levels; patients were excluded if they had severe respiratory impairment (FEV_1 < 40% predicted), liver enzymes 20% over ULN, or diabetes mellitus, were receiving oral steroids, or had significant steatorrhea, or asymptomatic gallstones	Improved height velocity, height-velocity *z* score, and height *z* score for bone age; improved bone age; improved weight velocity but no significant changes in BMI or LBM; decreased exercise endurance in 6 mo, but effect was reversed by 12 mo; pulmonary function improved but was not significant, and the number of pulmonary exacerbations was reduced; ADEs: minor bruising at injection sites was reported by patients; there were no changes in glucose parameters; there were transient increases in liver enzymes in 2 patients, but they resolved over time
Huseman et al[33] (1996) ($N = 9$)	Prospective; single group, all receiving rhGH	Fair	Product NR, 0.3 mg/kg per wk given 3 times weekly	9 mo in 1 patient; 12 mo in 8 patients	Prepubertal patients with CF aged 5.5–9.8 y and seen in outpatient clinic for at least the year before, during, and after rhGH therapy	Improved height velocity and height *z* scores; no significant changes in weight but increased arm muscle area and decreased arm fat area; improved bone age; pulmonary function improved but was not significant; positive nitrogen balance, suggesting improved muscle mass; ADEs NR; no significant change in routine chemistry values, including glucose values
Hardin and Sy[34] (1997) ($N = 24$)	Retrospective; observational registry database	Fair	NR	1.9 ± 1.3 y (mean ± SD)	Patients with CF in the National Cooperative Growth Study database who had not been previously treated with rhGH	Improved height and height velocity; improved weight-for-height *z* scores; ADEs: 2 patients (both girls who had progressed from Tanner stage 1 to 2) reported glucose intolerance

TABLE 2 Continued

Study	Study Design	Quality Rating	Product and Dose	Duration of Treatment	Population	Reported Results
Alemzadeh et al[35] (1998) ($N = 5$)	Prospective; single group, all receiving rhGH	Fair	Humatrope, 0.3 mg/kg per wk given daily 6 d of the week	2 y	Prepubertal patients with CF aged 6 mo to 5.2 y with pancreatic insufficiency and marked growth failure	Improved height and height *z* scores; improved weight and weight *z* scores; increased levels of IGF-I and IGFBP-3
Hardin et al[36] (1998) ($N = 9$)	Prospective; single group, all receiving rhGH	Fair	Somatotropin, 0.35 mg/kg per wk given daily	1 y	Prepubertal (Tanner stage 1) patients with CF aged 5.4–12.2 y	Improved height velocity and height *z* scores; improved weight velocity and LBM; pulmonary function trended toward improvement; ADEs: no changes in glucose parameters
Petrowsky et al[37] (2006) ($N = 1$)	Case report	Poor	Norditropin, 2.2 mg/d	3 y	18-y-old girl with CF who had previous lung transplantation and developed growth retardation	Developed pancreatic cancer, underwent pancreatic transplant; developed diabetes mellitus; died of metastases to liver
Stalvey et al[38] (2008) ($N = 2$)	Case report	Poor	Product NR, 0.3–0.35 mg/kg per wk	7–10 mo	5-y-old girl and 5-mo-old boy with CF and liver disease	5-y-old girl: improved height and weight, increased levels of IGF-I and IGFBP-3, liver transaminase levels normalized; 5-mo-old boy: improved height, weight, muscle mass, and tone, transitioned from total parenteral nutrition to enteral feeds

ULN indicates upper limit of normal; ADE, adverse drug event; NR, not reported; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor–binding protein 3.

control therapy as measured by the change in height, height velocity, and height *z* score. Results of observational studies or other trials not suitable for pooling support these findings. In 1 trial, the rhGH group experienced significant improvement from baseline in height percentile (baseline: 7.5 ± 1.2; 12 months: 20.0 ± 1.4; $P = .032$) but there were no significant changes in the control group (baseline: not reported; 12 months: 7.8 ± 1.6; $P = .64$).[14]

In controlled trials, significant improvements in weight were observed for patients with CF who received rhGH therapy versus control therapy as measured by change in weight, weight velocity, BMI, percent IBW, and lean body mass (LBM). Patients who received rhGH therapy had a trend toward a higher weight *z* score but did not have a higher BMI *z* score than those who received control therapy. In 1 trial, the rhGH group experienced a significant improvement in weight percentile (baseline: 4.0 ± 1.5; 12 months: 9.0 ± 1.3; $P = .042$), but there were no significant changes in the control group (baseline: not reported; 12 months: 3.5 ± 1.9; *P* value not reported).[14] Results of observational studies in which change in weight, weight velocity, and weight *z* score were evaluated were generally supportive of improvements associated with rhGH therapy, although the results of 1 crossover trial not amenable for pooling did not show any improvement in LBM for patients who received rhGH compared with those who received glutamine therapy.

In controlled trials and single-arm observational studies, treating patients with rhGH therapy does not improve bone age in patients with CF. However, bone mineral content (BMC) does significantly improve with rhGH therapy in trials, and BMC *z* score was also improved in the 1 trial in which it was assessed. At baseline, BMC *z* scores were −2.1 ± 0.6 in the rhGH group compared with −1.7 ± 0.9 in the control group; at 12 months, the rhGH group had a value of −1.4 ± 0.8 vs −1.7 ± 0.8 in controls.[26] The rhGH group had a statistically significant increase in BMC *z* score from baseline compared with controls ($P = .001$).

rhGH therapy in patients with CF does not seem to improve sexual maturation in boys, and the impact in girls cannot be determined at this time. Controlled trials were not amenable to pooling, and no single-arm observa-

TABLE 3 Summary of Results

Outcome	Type of Study	No. of Studies	Pooled-Effect Weighted Mean Difference (95% CI)	Conclusion	Strength of Evidence
KQ1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes including pulmonary function, growth (height, weight, LBM, protein turnover), exercise tolerance, and bone mineralization compared with usual care alone? pulmonary function, growth, exercise tolerance, and bone mineralization compared with usual care alone?					
Pulmonary function					
Absolute FVC	Controlled	3	0.67 L (0.24 to 1.09)	rhGH better than control	Moderate
	Single arm	1	NA	No effect	Insufficient
Percent predicted FVC	Controlled	5	9.34 (3.41 to 15.27)	rhGH better than control	Low
	Single arm	2	NA	Mixed results from baseline	Insufficient
Absolute FEV_1	Controlled	4	0.23 L (0.01 to 0.46)	rhGH better than control	Moderate
	Single arm	1	NA	No effect	Insufficient
Percent predicted FEV_1	Controlled	4	2.43 (−3.99 to 8.85)	No effect	Moderate
	Single arm	2	NA	No effect	Insufficient
FEV_1 *z* score	Controlled	1	−0.005 (−0.22 to 0.21)	No effect	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Anthropometrics					
Height	Controlled	3	3.13 cm (0.88 to 5.38)	rhGH better than control	Low
	Single arm	1	NA	Improvement from baseline	Insufficient
Height velocity	Controlled	3	3.27 cm/y (2.33 to 4.21)	rhGH better than control	Moderate
	Single arm	4	NA	Improvement from baseline	Insufficient
Height *z* score	Controlled	3	0.51 (0.35 to 0.66)	rhGH better than control	Moderate
	Single arm	3	NA	Improvement from baseline	Low
Height percentile	Controlled	1	NA	rhGH better than control	Insufficient
	Single arm			No data are available	NA
Weight	Controlled	5	1.48 kg (0.62 to 2.33)	rhGH better than control	Moderate
	Single arm	1	NA	Improvement from baseline	Insufficient
Weight velocity	Controlled	2	2.15 kg/y (1.52 to 2.78)	rhGH better than control	Moderate
	Single arm	3	NA	No effect	Low
Weight *z* score	Controlled	4	0.49 (−0.02 to 1.00)	No effect	Low
	Single arm	1	NA	Improvement from baseline	Insufficient
Weight percentile	Controlled	1	NA	rhGH better than control	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
BMI	Controlled	2	2.08 (1.20 to 2.96)	rhGH better than control	Moderate
	Single arm	1	NA	No effect	Insufficient
BMI *z* score	Controlled	1	−0.05 (−0.30 to 0.20)	No effect	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Percent IBW	Controlled	2	12.57 (7.01 to 18.12)	rhGH better than control	Low
	Single arm	No data are available	No data are available	No data are available	Insufficient
LBM	Controlled	8	1.92 kg (1.47 to 2.37)	rhGH better than control	Moderate
	Single arm	No data are available	No data are available	No data are available	Insufficient

TABLE 3 Continued

Outcome	Type of Study	No. of Studies	Pooled-Effect Weighted Mean Difference (95% CI)	Conclusion	Strength of Evidence
Exercise tolerance: various	Controlled	3	NA	No effect	Insufficient
	Single arm	1	NA	No effect	Insufficient
Bone mineralization					
Bone age	Controlled	2	NA	No effect	Insufficient
	Single arm	3	NA	No effect	Low
BMC	Controlled	4	192 g (110 to 273)	rhGH better than control	Low
	Single arm	No data are available	No data are available	No data are available	Insufficient
BMC *z* score	Controlled	1	No	rhGH better than control	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Sexual maturation	Controlled	7	NA	rhGH better than control	Low
	Single arm	No data are available	No data are available	No data are available	Insufficient
KQ2: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes including frequency of required intravenous antibiotic treatments, frequency of hospitalization, quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality compared with usual care alone?					
Antibiotic usage	Controlled	3	NA	rhGH better than control	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Pulmonary exacerbations	Controlled	1	NA	No effect	Insufficient
	Single arm		No data are available	No data are available	Insufficient
Hospitalization rate	Controlled	4	−1.62 events per y (−1.98 to −1.26)	rhGH better than control	Moderate
	Single arm	No data are available	No data are available	No data are available	Insufficient
HRQoL	Controlled	2	NA	rhGH better than control	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Bone consequences	No data are available	No data are available	No data are available	No data are available	Insufficient
Mortality	No data are available	No data are available	No data are available	No data are available	Insufficient
KQ3: In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH? Adverse effects of interest include, but are not limited to, glucose intolerance, diabetes, and hypoglycemia.					
Glucose parameters					
A1c	Controlled	2	−0.10 (−0.40 to 0.20)	No effect	Low
	Single arm	2	NA	No effect	Low
Random BG	Controlled	3	NA	Glucose levels remained stable	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Fasting BG	Controlled	2	5.68 mg/dL (0.43 to 10.93)	Increased with rhGH compared to control	Moderate
	Single arm	1	NA	No effect	Insufficient
Stimulated BG	Controlled	1	4.93 mg/dL (−15.13 to 24.98)	No effect	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient

TABLE 3 Continued

Outcome	Type of Study	No. of Studies	Pooled-Effect Weighted Mean Difference (95% CI)	Conclusion	Strength of Evidence
Postprandial BG	Controlled	1	NA	No effect	Insufficient
	Single arm	No data are available	No data are available	No data are available	Insufficient
Glucose intolerance	Controlled	7	NA	No patients developed	Low
	Single arm	3	NA	Few patients developed	Insufficient
Diabetes	Controlled	7	NA	No patients developed	Low
	Single arm	1	NA	1 case report of diabetes	Insufficient
Injection site reactions	Controlled	No data are available	No data are available	No data are available	NA
	Single arm	2	NA	Minor discomfort and bruising reported	NA
Liver transaminases	Controlled	No data are available	No data are available	No data are available	NA
	Single arm	2	NA	Limited report of liver transaminase level elevations	NA
Study withdrawals	Controlled	10	NA	Majority of trials reported no withdrawals	NA
	Single arm	No data are available	No data are available	No data are available	NA
KQ4: In patients with CF, how are efficacy, effectiveness, safety, and adverse events affected by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?					
Dose	Controlled	1	NA	No significant differences between dose groups in end points	NA
Duration	Controlled	9	See Table 6	1-y therapy trends toward improved efficacy vs 6-mo therapy; 1-y therapy trends toward increased glucose parameters vs 6-mo therapy	NA
Baseline nutritional status	Controlled	1	NA	There is limited evidence in patients with variable nutritional status; efficacy exists in patients who received enteral nutrition	NA
Concurrent medical therapies	Controlled	No data are available	No data are available	No data are available	NA

TABLE 3 Continued

Outcome	Type of Study	No. of Studies	Pooled-Effect Weighted Mean Difference (95% CI)	Conclusion	Strength of Evidence
KQ5: In patients with CF, how do the efficacy, effectiveness, safety, and adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to, age (prepubertal, pubertal, postpubertal), gender, baseline clinical status (height, weight, LBM, pulmonary function, exercise tolerance, nutritional status), and/or the nature, extent, and effectiveness of previous treatment.					
Age	Controlled	6	See Table 5	Pubertal patients may derive greater benefit in pulmonary function, weight, and BMC than prepubertal patients; prepubertal patients may derive greater benefit in height than pubertal patients	NA
Gender	Controlled	3	NA	Girls (both prepubertal and pubertal) may experience greater benefit in height and weight than boys	NA
Baseline clinical status	Controlled	2	NA	Patients with lower baseline height *z* scores experienced greater height improvement than those with higher height *z* scores; higher baseline weight was correlated with greater improvement in pulmonary function	NA
Previous treatment				No data are available	NA

CI indicates confidence interval; KQ, key question; NA, not applicable; BG, blood glucose.
[a] Pooled by Vanderwel and Hardin.[27]

tional data were available. In 5 controlled trials, rhGH therapy did not improve sexual maturation regardless of gender. In 1 controlled trial, mean Tanner stage regardless of gender improved, and in an analysis of 3 controlled trials, rhGH therapy significantly improved sexual maturation in girls but not in boys.

Key Question 2

There is insufficient evidence to determine the effect of rhGH on most final health outcomes. Preliminary data suggest that rhGH may have a benefit on intravenous antibiotic use. However, there is insufficient evidence to determine the effect of rhGH on pulmonary exacerbations, HRQoL, bone consequences, or mortality. There is moderate evidence to suggest that rhGH therapy reduces the rate of hospitalization.

Key Question 3

In 2 controlled trials suitable for pooling therapy with rhGH does not impact glycosylated hemoglobin A1c (A1c) in patients with CF. In patients with CF, rhGH therapy significantly increases fasting blood glucose concentrations in 3 controlled trials but does not significantly alter random, postprandial, and stimulated blood glucose concentrations. Most patients with CF who received rhGH did not develop glucose intolerance or diabetes over the duration studied (6 to 12 months) in 5 controlled trials or 3 single arm observational studies.

In patients with CF who received rhGH, injection-site reactions were a rare and insignificant adverse effect. Patients with CF on rhGH may rarely ex-

perience a transient increase in liver transaminase levels. Study withdrawals were rare in trials that evaluated rhGH in patients with CF. These endpoints could not be rated for strength of evidence given the paucity of data available.

Key Question 4

Only 1 trial provided insight into the dose-response nature of rhGH in patients with CF. In that trial, no significant differences were seen between the higher- and lower-dose groups for any evaluated parameter.

Several trials varied in the duration of rhGH therapy, allowing subgroup analysis based on therapy duration (Table 4). Trials with 1 year of rhGH therapy significantly increased percent predicted FVC, absolute FEVI, and height compared to control, while 6 months of rhGH therapy showed no effect. Trials with 1 year of rhGH therapy significantly increased fasting glucose concentrations, while trials of 6 months duration showed no effect.

rhGH has not been studied in patients with CF who have nutritional deficiencies that are not being addressed with enteral nutrition. We cannot determine the benefits of rhGH therapy in patients with unaddressed nutritional deficiencies.

The usage of concurrent medical therapies in patients enrolled in trials that evaluated rhGH therapy was sparingly reported, so the differential effect on rhGH efficacy could not be assessed.

Key Question 5

A patient's age may affect rhGH efficacy, as seen in an individual-patient data-merged analysis and subgroup analysis (Table 5). In an individual-patient data-merged analysis of trials, both prepubertal and adolescent patients had significant improvements in height, weight, LBM, and hospitalizations compared with their respective control populations. Prepubertal patients who received rhGH did not have significant increases in FEV_1, and the percent predicted FEV_1 was significantly lower than that in prepubertal control patients. In contrast, adoles-

TABLE 4 Subgroup Analyses Based on Duration of rhGH therapy

Outcome	Trials With 6-Mo Duration, Pooled Effect (95% CI)	Trials With 1-y Duration, Pooled Effect (95% CI)
Pulmonary outcome		
Absolute FVC, L	NR	0.67 (0.24 to 1.09)
Percent predicted FVC	5.29 (−2.14 to 12.72)	11.37 (3.18 to 19.57)
Absolute FEV_1, L	0.04 (−0.16 to 0.24)	0.36 (0.06 to 0.66)
Percent predicted FEV_1	2.89 (−7.69 to 13.47)	2.16 (−5.91 to 10.23)
Anthropometrics		
Height, cm	1.40 (−0.07 to 2.87)	4.32 (3.03 to 5.62)
Height velocity, cm/y	2.56 (1.11 to 4.01)	3.65 (2.19 to 5.10)
Height *z* score	NR	0.51 (0.35 to 0.66)
Weight, kg	0.93 (0.08 to 1.78)	2.50 (0.48 to 4.51)
Weight velocity, kg/y	NR	2.15 (1.52 to 2.78)
Weight *z* score	NR	0.49 (−0.02 to 1.00)
BMI	NR	2.08 (1.20 to 2.96)
BMI *z* score	−0.05 (−0.30 to 0.20)	NR
Percent IBW	NR	12.57 (7.01 to 18.12)
LBM, kg	1.57 (0.65 to 2.49)	2.05 (1.50 to 2.60)
Bone outcome: BMC, g	NR	192 (110 to 273)
Exercise tolerance, exercise work rate, W	8.08 (−2.76 to 18.91)	31.90 (4.54 to 59.26)
Final health outcome, hospitalizations, events per y	NR	−1.62 (−1.98 to −1.26)
Glucose parameters		
A1c, %	NR	−0.10 (−0.40 to 0.20)
Fasting BG, mg/dL	3.89 (−2.62 to 10.41)	9.00 (0.11 to 17.89)
Stimulated BG, mg/dL	4.93 (−15.13 to 24.98)	NR

CI indicates confidence interval; BG, blood glucose; NR, not reported.

TABLE 5 Subgroup Analyses Based on Pubertal Status of Patients Enrolled

Outcome	Controlled Trials That Only Enrolled Prepubertal Patients, Pooled Effect (95% CI)	Controlled Trials That Only Enrolled Pubertal Patients, Pooled Effect (95% CI)
Pulmonary outcome		
Absolute FVC, L	0.55 (0.10 to 1.00)	1.00 (0.32 to 1.68)
Percent predicted FVC	17.49 (−7.00 to 42.00)	12.70 (11.30 to 14.10)
Absolute FEV_1, L	0.28 (−0.03 to 0.58)	0.64 (0.05 to 1.23)
Percent predicted FEV_1	3.25 (−8.54 to 15.03)	NR
Anthropometrics		
Height, cm	4.40 (2.95 to 5.85)	3.90 (0.52 to 7.28)
Height velocity, cm/y	3.65 (2.19 to 5.10)	NR
Height *z* score	0.51 (0.35 to 0.66)	NR
Weight, kg	1.78 (0.04 to 3.53)	5.50 (1.76 to 9.24)
Weight velocity, kg/y	2.15 (1.52 to 2.78)	NR
Weight *z* score	0.74 (0.34 to 1.14)	NR
BMI	1.60 (0.95 to 2.25)	2.50 (2.07 to 2.93)
BMI *z* score	NR	NR
Percent IBW	10.00 (5.74 to 14.26)	15.70 (10.30 to 21.10)
LBM, kg	2.04 (1.43 to 2.64)	NR
Bone outcome: BMC, g	144 (68 to 220)	650 (427 to 873)
Exercise tolerance: exercise work rate, W	NR	NR
Final health outcome: hospitalizations, events per y	−1.49 (−1.96 to −1.02)	−1.81 (−2.38 to −1.24)
Glucose parameter		
A1c, %	−0.10 (−0.46 to 0.26)	−0.10 (−0.64 to 0.44)
Fasting BG, mg/dL	9.00 (0.11 to 17.89)	NR
Stimulated BG, mg/dL	NR	NR

CI indicates confidence interval; BG, blood glucose; NR, not reported.

cent patients who received rhGH had significant improvements in FEV_1 and percent predicted FEV_1 compared with adolescent control patients. In a pooled analysis that should only be viewed as hypothesis-generating, prepubertal patients who received rhGH seemed to derive greater benefits on height than pubertal patients who received rhGH but derived lesser benefits on weight, BMI, and percent IBW. Pubertal patients who received rhGH also seemed to derive greater increases in absolute FVC, FEV_1, and BMC but experienced fewer hospitalizations and smaller increases in percent predicted FVC than prepubertal patients.

Although most trials were conducted predominantly in males, the impact of gender on outcomes of rhGH therapy could be qualitatively assessed in 1 pooled analysis. The authors of the analysis did not report *P* values or whether the comparisons were statistically significant and did not provide patient numbers, which precluded our ability to calculate these *P* values. In prepubertal patients who did not receive rhGH therapy, no difference in height velocity occurred between the genders in the year before treatment allocation, but girls had greater weight velocity. In pubertal patients who did not receive rhGH therapy, girls had greater height and weight velocity than boys in the year before treatment allocation. In prepubertal patients, the first 6 months of rhGH therapy provided similar increases in height and weight velocity between genders, but in months 6 to 12 girls had greater height velocity whereas boys had greater weight velocity. In pubertal patients, the first 6 months of rhGH therapy provided similar increases in height velocity between genders, but girls had greater increases in weight velocity. In months 6 to 12, the girls had greater height and weight velocities than the boys. The occurrence of adverse effects associated with rhGH therapy in boys and girls was not individually determined.

The impact of baseline clinical status on clinical outcomes of rhGH therapy was assessed in 2 trials. In the first trial, those with a baseline height *z* score below −2.2 had a similar increase in height *z* score on rhGH therapy as those with higher baseline *z* scores. In the second trial, a higher baseline percent predicted FEV_1 was positively correlated with the change of weight associated with rhGH therapy. The occurrence of adverse events associated with rhGH therapy in patients with different baseline clinical statuses could not be determined.

DISCUSSION

rhGH qualitatively improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF. Improvements in BMC are also promising. However, with the exception of hospitalizations, the benefits on final health outcomes cannot be directly determined at this time. When relatively low-dose rhGH therapy is given to patients with CF for 6 to 12 months, it may worsen short-term markers of glucose control but has no effect on A1c.

Although rhGH is a promising therapy for the treatment of CF, there are a number of important research questions that should be answered before its role can truly be discerned. In our analysis, we found improvements in height, weight, BMC, and a few but not all measures of pulmonary function with rhGH therapy, but we do not know if this translates into significantly fewer pulmonary exacerbations or infections, deaths, or bone fractures or if therapy improves HRQoL in a meaningful way. Most of the trials compared rhGH therapy to no therapy rather than to placebo or an active control and did not rigorously assess for harms. Although study results have suggested that the risk of glucose-metabolism problems with rhGH is low (on the basis of A1c concentrations), longer durations of therapy may increase the risk of glucose intolerance more than shorter durations (on the basis of glucose concentrations).

Our systematic review and meta-analysis was limited by the available literature. To date, results of the randomized controlled trial conducted by Stalvey et al[30] have not been published, and data are only available in abstract form. We opted to include these valuable data in our analysis because of the small numbers of controlled trials available. Second, we included both randomized controlled trials and observational cohort studies in the category of controlled trials because both sets of studies compared rhGH therapy to a control group. In addition, in their retrospective study report, Hardin et al[24] described prospective follow-up methods similar to those seen in randomized controlled trials. In some cases, the extrapolation of numerical data from figures was necessary to report and analyze the data when numerical data were not available either in the article or by contacting the authors. Data were extracted from figures in duplicate after digitally enlarging figures and superimposing gridlines.

The data that linked improvements in pulmonary function with reductions in final health outcomes in patients with CF were most apparent with percent predicted FEV_1. However, treatment with rhGH only nonsignificantly increases percent predicted FEV_1. In addition, preliminary data suggest that pubertal/adolescent patients may derive more pulmonary benefits from rhGH therapy than prepubertal patients, although there are dissimilar increases in height. This suggests that improvements in pulmonary function

may not be tied directly to improvements in height and that the target population for rhGH therapy needs to be refined further.

For patients with osteoporosis but without CF, therapy with bisphosphonates improves bone mineralization and reduces the risk of bone fractures.[39] However, sodium fluoride treatment dramatically increases BMC but may not reduce the risk of vertebral fractures and in high doses may increase the risk of nonvertebral fractures.[39] As such, it cannot be simply assumed that improvements in bone mineralization derived from rhGH therapy in patients with CF will reduce the risk of bone fractures and complications such as death.[39]

With the above-mentioned limitations in mind, we propose several avenues for future research. An individual-patient data meta-analysis of completed trials that evaluated rhGH therapy in patients with CF would yield important information if original trial investigators were willing to report on hospitalizations, deaths, or bone fractures. An individual-patient data meta-analysis could allow the determination of the benefits of rhGH therapy in patients with varying levels of nutritional status, pubertal status, age, and concurrent medical therapy, all of which are important unresolved issues. A large, multicenter, randomized, placebo-controlled trial should be conducted to determine the impact of rhGH therapy on hospitalizations, mortality, bone fractures, and HRQoL. Such a trial should be powered and conducted to analyze data in pubertal and prepubertal patients separately. Even if a large multicenter trial is not feasible, we suggest that smaller future trials that evaluate the impact of rhGH in patients with CF be placebo controlled and prospectively collect data on hospitalizations, mortality, bone fractures, and HRQoL and report on their results even if they are not powered to be quantitatively analyzed. Trials with treatment durations of 6 or 12 months or longer would be helpful in subsequently determining the adequate duration of therapy.

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