Effective Health Care Program

Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis

Executive Summary

Background

Cystic fibrosis (CF) is the second most common life-shortening, childhood-onset genetic disease in the United States, affecting approximately 30,000 people in the Nation. The gene responsible for CF encodes the cystic fibrosis transmembrane regulator (CFTR) protein, which regulates sodium and chloride transport across epithelial membranes. This affects nearly all exocrine glands, with abnormally viscous mucus and excessive secretions. The dominant clinical features are chronic lung disease and pancreatic insufficiency with poor nutrition and growth.

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 2006 (37-year survival).

Growth and nutritional indexes (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. Both poor weight

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The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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and shorter height have also been shown to be independently associated with increased morbidity and mortality in CF patients in some studies.

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 U.S. Food and Drug Administration include the treatment of growth hormone deficiency, idiopathic short stature, Turner syndrome, Prader-Willi syndrome, and chronic renal insufficiency, and treatment of children who are small for gestational age. It has been investigated for the treatment of CF because of the decreased growth measures and increased energy expenditures in CF patients.

Scope and Key Questions

This Comparative Effectiveness Review, prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC), examines the benefits and harms associated with using rhGH in patients with CF. The key questions examined are:

Key Question 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function; growth (height, weight, lean body mass [LBM], protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?

Key Question 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?

Key Question 3: In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?

Key Question 4: 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.

Key Question 5: What is the risk of malignancy associated with rhGH use as determined by (a) markers of cancer risk with rhGH (insulin-like growth factor-I [IGF-I] increases over 100 ng/ml or insulin-like growth factor binding protein-3[IGFBP-3] decreases over 1,000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2 mg/kg/week to 0.6 mg/kg/week) for disorders such as growth hormone deficiency (GHD) and idiopathic short stature (ISS)?

Key Question 6: In patients with CF, how are efficacy, effectiveness, safety, or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?

Key Question 7: In patients with CF, how do the efficacy, effectiveness, safety, or 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 prior treatment.

Methods

Literature Search Strategy

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. Three separate searches were conducted. The first search was used to identify trials and studies that explicitly evaluated the impact of rhGH on outcomes in patients with CF. The two other searches were used to answer questions regarding the impact of intermediate health outcomes on final health outcomes in patients with CF and evaluated the potential for malignant effects of rhGH as assessed in a CF population and those with ISS or GHD. In these two additional searches, we utilized Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008) to limit the search to randomized controlled trials and the Scottish Intercollegiate Guidelines Network

Observational Study Search Filter to limit the search to observational studies. No language restrictions were imposed, and a manual search of references from reports of clinical trials or review articles was conducted.

Study Selection

Studies were included in the evaluation of Key Questions 1, 2, 4, 6, and 7 if they were (1) studies of rhGH therapy; (2) studies conducted in patients with CF; (3) studies that reported data on prespecified clinical or humanistic outcomes; and (4) reports of new discovery (specifically, randomized controlled trials, observational trials, systematic reviews/meta-analyses, or case reports). Studies were included in the Key Question 3 evaluation if they were (1) conducted in patients with CF; (2) either randomized controlled trials or observational studies; and (3) studies that reported linkages between intermediate outcomes and health outcomes. Studies that reported on linkages between intermediate and final health outcomes subsequent to a medical or behavioral intervention were excluded from this evaluation. Studies were included in the Key Question 5 evaluation if they were (1) studies of rhGH therapy; (2) studies conducted in patients with CF, ISS, or GHD; (3) either randomized controlled trials or observational studies; and (4) studies that reported data on malignant outcomes.

Data Abstraction

Through the use of a standardized data abstraction tool, two reviewers independently collected data, with disagreement resolved through discussion. The following information was obtained from each trial, if applicable: author identification; year of publication; source of study funding; study design characteristics and methodological quality criteria; study population (including study inclusion and exclusion criteria, run-in period, study withdrawals, dose of rhGH utilized, length of study, duration of patient followup, and disease state [CF, ISS, or GHD]); patient baseline characteristics (gender, age, ethnicity, nutritional status); comorbidities; and use of concurrent standard medical therapies (corticosteroids, antibiotics, etc.). Endpoints included pulmonary function; anthropometrics (height, weight, LBM, protein turnover); 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.

Literature Synthesis

Regarding the intermediate outcomes within Key Question 1, there are distinct clusters of outcomes that may be reported in a variety of ways. For pulmonary function, trials and studies report a wide range of outcomes, such as absolute values of FEV_1 and forced vital capacity (FVC), along with the percent predicted FEV_1 and FVC. The most commonly reported of these were selected for meta-analysis, while the remaining outcomes were reported qualitatively. Anthropometrics are also reported in many ways, including absolute values of height, height percentiles, height Z-scores, height velocity, absolute values of weight, weight percentiles, weight Z-scores, weight velocity, and weight-for-height Z-scores. Those endpoints amenable to meta-analysis were quantitatively synthesized and the rest were qualitatively described.

Final health outcomes in Key Question 2 and harms in Key Question 4 associated with rhGH were meta-analyzed where appropriate and the rest were qualitatively described. The remaining Key Questions (3, 5-7) were not amenable to quantitative synthesis and were answered qualitatively.

Quantitative Analysis

Randomized controlled trials and prospective cohort studies were pooled together when trials evaluated both an rhGH and a control group; they are henceforth described as controlled trials. Single-arm observational studies were described qualitatively in all cases.

When pooling continuous endpoints, a weighted mean difference (WMD) was calculated using a DerSimonian and Laird random-effects model. In cases where mean change scores from baseline for each group were not reported, we calculated the difference between the mean baseline and mean followup scores for each group. Standard deviations (SDs) of the change scores were calculated using the method proposed by Follman and colleagues. In the event that there was more than one treatment group vs. 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 endpoints, weighted averages were

reported as relative risks (RRs) with associated 9-percent confidence intervals (CIs). As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating RRs and 9-percent CIs.

Statistical heterogeneity was addressed using the $I2$ statistic, which assesses the degree of inconsistency across studies not due to chance. It ranges from 0-100 percent, with values of 25 percent, 50 percent, and 75 percent representing 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 performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd., Cheshire, England). A p-value of <0.05 was considered statistically significant for all analyses.

Subgroup and Sensitivity Analyses

To assess the effect of heterogeneity on our meta-analysis conclusions, subgroup and sensitivity analyses were conducted. Subgroup analyses were conducted to assess the effect of treatment duration and patient pubertal status on the efficacy of rhGH. Trials with a duration of 6 months were meta-analyzed separately from trials with a duration of 1 year. Trials that enrolled prepubertal patients were meta-analyzed and compared to the one trial that enrolled pubertal patients alone. Trials that enrolled patients with a range of pubertal status were excluded from subgroup analysis.

Results

When conducting the literature search to identify articles that evaluated the use of rhGH in CF populations, we retrieved 44 unique citations and another citation was identified from other sources. Eighteen articles were excluded during the title and abstract review, and two articles were excluded during the full-text review. A total of 26 articles were found to match our inclusion criteria.

From the literature search for studies that evaluated the linkages between intermediate and final health outcomes, we retrieved 1,126 unique citations. An additional 16 references were obtained from other sources. After a review of the titles and abstracts, 113

were deemed eligible for further review, and the full articles were retrieved. A total of 53 articles were found to match our inclusion criteria. Three studies reported on the same population in another included publication; and they were included, as they provided additional data. Therefore, a total of 50 unique studies were included in our evaluation.

When we conducted the literature search for cancer in non-CF populations, 159 unique citations were retrieved and another 2 citations were identified through other sources. One hundred sixteen citations were excluded during the title and abstract review and 44 during the full-text review. Three articles were included.

A summary of the results and the strength of evidence for all key questions can be found in Table A.

Key Question 1

Controlled trials were limited to patients with CF and impaired baseline growth indexes. Five markers of pulmonary function were evaluated in patients with CF receiving rhGH therapy. In controlled trials, the FVC and percent predicted FVC significantly increased from baseline in with CF receiving chronic rhGH therapy vs. control therapy. Single-arm observational studies support these findings. In controlled trials, the FEV_1 significantly increased from baseline in patients with CF receiving chronic rhGH therapy vs. control therapy, while the percent predicted FEV_1 showed no significant differences vs. control. Single-arm observational studies support the FEV_1 findings, but the findings on percent predicted FEV_1 are mixed. In the one available controlled trial, no change in FEV_1 Z-score occurred in patients receiving rhGH for CF vs. 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 receiving rhGH therapy vs. control therapy as measured by the change in height, height velocity, height Z-score, and height percentile. Observational studies or other trials not suitable for pooling support these findings. In controlled trials, significant improvements in weight were observed for patients with CF receiving rhGH therapy vs. control therapy, as measured by change in weight, weight velocity, body mass index (BMI), percent IBW, LBM, and weight percentile. Patients receiving rhGH therapy had a trend

toward a higher weight Z-score but did not have a higher BMI Z-score than those receiving control therapy. Observational studies evaluating change in weight, weight velocity, and weight Z-score were generally supportive of improvements associated with rhGH therapy, although one crossover trial not amenable to pooling did not show any improvement in LBM in patients receiving rhGH compared with those who received glutamine therapy.

Four markers of protein turnover were evaluated in patients with CF receiving rhGH therapy. In controlled trials, rhGH therapy significantly improved two markers of protein turnover (rate of leucine oxidation [LeuOx] and rate of nonoxidative leucine disappearance [NOLD]) and had no effect on leucine rate of appearance (LeuRa) concentrations. In one observational trial, nitrogen balance was qualitatively impacted but protein synthesis was unchanged. In controlled trials, rhGH therapy significantly improved exercise workrate. Qualitative improvements in several measures of exercise tolerance were seen after rhGH therapy in patients with CF but in most cases do not reach statistical significance. Given the few trials evaluating this type of endpoint and the various markers being evaluated, the impact is difficult to determine at this time.

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 did significantly improve with rhGH therapy in trials, and bone mineral content Z-score was also improved in the one trial in which it was assessed.

In patients with CF, rhGH therapy does not seem to improve sexual maturation in males and the impact in females cannot be determined at this time. Controlled trials were not amenable to pooling, and no single-arm observational data were available. In five controlled trials, rhGH therapy did not improve sexual maturation regardless of gender. In one controlled trial, mean Tanner stage improved regardless of gender, and in an analysis of three controlled trials, rhGH therapy significantly improved sexual maturation in females but not in males.

Key Question 2

There is insufficient evidence to determine the effect of rhGH on final health outcomes. Preliminary data suggest that rhGH may have benefit regarding 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

The association between pulmonary function and mortality in patients with CF was evaluated in 28 studies. Only one of three studies that evaluated FVC at baseline and mortality found a univariate association, and only two of five that evaluated percent predicted FVC at baseline and mortality found a univariate association. However, only one of the aforementioned studies performed multivariate analysis; that study found that percent predicted FVC at baseline was a multivariate predictor. Decrease in FVC was a univariate and multivariate predictor of mortality in two trials but not in two other trials. Some studies using univariate analysis found an association between measures of absolute FEV_1 and mortality, but other studies did not. In the only two multivariate analyses, an association was found between FEV_1 and mortality in one study, but no association was seen between the decline in FEV_1 and mortality. The link between percent predicted FEV_1 and mortality is stronger, with a majority of studies finding an association between percent predicted FEV_1 and mortality.

The association between anthropometrics and mortality in patients with CF was evaluated in 26 studies. The link between height and mortality is weak with only a minority of studies reporting an association. The link between different measures of weight and mortality was supported in a majority of studies that performed univariate analysis. Only one study found a multivariate relationship between weight and mortality, and another multivariate analysis did not. The link between BMI and mortality is controversial, with some studies showing no association, others showing only a univariate association, and very few showing a multivariate association. The link between IBW and mortality was supported by several univariate

associations and in the only multivariate analysis. The only study evaluating the association between percent predicted weight-for-height and mortality found a multivariate association.

No studies evaluated the association between protein turnover and mortality.

The association between exercise tolerance and mortality in patients with CF was evaluated in 10 studies. The link between walk testing and mortality is weak, with some studies finding no association, some finding only a univariate association, and very few finding a multivariate association. The link between peak oxygen uptake during exercise testing and mortality was supported only by univariate analyses.

No studies evaluated the association between bone mineralization and mortality.

The association between pulmonary function and HRQoL in patients with CF was evaluated in 14 studies, but 10 different scales were used. All studies but one specified that they explored the association between percent predicted FEV_1 and HRQoL. The last study did not specify whether the FEV_1 was absolute or percent predicted. Only four studies employed multivariate analyses (each using different questionnaires to rate HRQoL). In one multivariate analysis, higher percent predicted FEV_1 was associated with improvements in "ways of coping" but not subjective health perception, and it was not specified whether absolute or percent predicted FEV_1 was used. Higher percent predicted FEV_1 was associated with improvements in seven of nine health domains (including social and physical functioning and chest symptoms) in another study, and with general well-being in another study, but no association was seen between FEV_1 and general health perception in the final study.

The association between anthropometrics and HRQoL in patients with CF was evaluated in 10 studies, but nine different scales and different anthropometric parameters were used. Only five studies employed multivariate analyses (each using different questionnaires to rate HRQoL). In multivariate analysis, greater percent IBW was not associated with subjective health perception or coping in one study; greater BMI was associated with improvements in body image but

not any other factor, including social and physical functioning and chest symptoms, in another study; adequate weight gain over 2 years was associated with improvements in physical functioning but not social or emotional functioning; BMI Z-score was not associated with any of the three dimensions in one study; greater BMI was associated with lower general health perception in one study; and BMI was not associated with life satisfaction.

No studies evaluated the association between protein turnover and HRQoL.

Two studies evaluated the association between exercise tolerance and HRQoL using two different questionnaires. Greater exercise capacity (determined by peak oxygen uptake [VO_{2peak}] or maximal workload) is associated with better measures of HRQoL scores in univariate analyses.

No studies evaluated the association between bone mineralization and HRQoL.

Only one study evaluated the association between pulmonary function or anthropometrics and bone consequences. In univariate analyses, there was no relationship between FEV_1, FVC, or BMI and bone fracture.

No studies evaluated the association between protein turnover, exercise tolerance, or bone mineralization and bone consequences.

Key Question 4

In two controlled trials suitable for pooling, therapy with rhGH did not impact A1c in CF patients vs. control. In CF patients, rhGH therapy significantly increased fasting blood glucose concentrations vs. control in three controlled trials but did not significantly alter random, postprandial, and stimulated blood glucose concentrations vs. control or baseline. Most CF patients receiving rhGH in five controlled and three single-arm observational studies did not develop glucose intolerance or diabetes over the duration studied (6-12 months). The strength of evidence was moderate for the fasting blood glucose evaluation; low for the A1c, glucose intolerance, and diabetes mellitus evaluations; and insufficient for the other endpoints.

In CF patients receiving rhGH, injection site reactions were a rare adverse effect reported in observational studies. CF patients on rhGH rarely experienced a transient increase in liver transaminases in two single-arm observational studies. Study withdrawals were rarely reported in the nine trials with evaluable data, and withdrawals in patients with CF receiving rhGH were similar to control. These endpoints could not be rated for strength of evidence, given the paucity of data available.

Key Question 5

In patients with CF, there appears to be an increase in IGF-I levels in patients treated with rhGH compared to control, but the strength of evidence is insufficient. There is insufficient evidence to determine the impact of rhGH treatment on IGFBP-3 levels. In patients with GHD or ISS, there is little evidence to evaluate the effects of rhGH treatment on cancer risk.

Key Question 6

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

Several trials varied in the duration of rhGH therapy, allowing subgroup analysis based on therapy duration. Trials with 1 year of rhGH therapy significantly increased percent predicted FVC, absolute FEV_1, 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.

Use of 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 evaluating rhGH therapy was sparingly reported, so the differential effect on rhGH efficacy could not be assessed.

Key Question 7

A patient's age may impact rhGH efficacy, as seen in an analysis with individual patient data merged and in a subgroup analysis. In an analysis of trials with individual patient data merged, both prepubertal and adolescent patients had significant improvements in height, weight, LBM, and hospitalizations compared with their respective control populations. Prepubertal patients receiving rhGH did not have significant increases in FEV_1, and the percent predicted FEV_1 was significantly lower than for prepubertal control patients. In contrast, adolescent patients receiving rhGH had significant improvements in FEV_1 and percent predicted FEV_1 compared with adolescent control patients.

When we pooled studies limited to prepubertal patients and then pooled the trials limited to pubertal patients, we noted some differences in magnitude of effect with rhGH vs. control between populations. Given inherent limitations in cross-evaluating between these two controlled study types, the following observations should be viewed only as hypothesis generating. Compared with pubertal patients receiving rhGH, prepubertal patients receiving rhGH seem to derive greater benefits in height vs. control but lesser benefits in weight, BMI, and percent IBW vs. control. Compared with prepubertal patients receiving rhGH, pubertal patients receiving rhGH seem to derive greater increases in absolute FVC, FEV_1, and bone mineral content vs. control but experience fewer hospitalizations and smaller increases in percent predicted FVC.

While most trials were conducted predominantly in males, the impact of gender on outcomes of rhGH therapy could be evaluated in one 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, precluding our ability to calculate these p-values. In prepubertal patients not receiving rhGH therapy, no difference in height velocity occurred between the genders in the year before treatment allocation, but females had greater weight velocity. In pubertal patients not receiving rhGH therapy, females had greater height and weight velocity than males 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, females had greater height velocity while males had greater weight velocity. In pubertal patients, the first 6 months of rhGH therapy provided similar increases in height velocity between genders, but females had greater increases in weight velocity. In months 6 to 12, females had greater height and weight velocities than males. The occurrence of adverse effects associated with rhGH therapy in males and females was not individually determined.

The impact of baseline clinical status on the clinical outcomes of rhGH use was assessed in two 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. 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 status could not be determined.

Conclusions

In patients with CF and impaired baseline growth indexes, rhGH improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF vs. control. Improvements in bone mineral content vs. control are also promising. However, with the exception of hospitalizations, the benefits on final health outcomes cannot be directly determined at this time. In the relatively low doses used in CF patients for a time period of 6 to 12 months, rhGH therapy may worsen short-term markers of glucose control but has no effect on A1c vs. control. The increase in IGF-I with rhGH therapy is above a threshold thought to increase the risk of malignancy, but the strength of this marker in determining malignancy is not firmly established. A time period of 6 to 12 months may be insufficient to determine the effect of rhGH on development of diabetes or malignancy.

Future Research

Individual Patient Data Meta-Analysis

- We believe that an individual patient data meta-analysis of completed trials evaluating rhGH therapy in patients with CF would yield important information if original trial investigators were willing to report on hospitalizations, deaths, or bone fractures. We attempted to contact all the authors and explicitly ask for any information they had on these final health outcomes but were unsuccessful.

- 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 important unanswered questions.

Clinical Trials

- We believe that 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.

  - It may be worthwhile for the Cystic Fibrosis Foundation and key trialists to appoint a working group and establish a network of sites interested in prospectively evaluating the impact of rhGH in patients with CF so that such a trial could be conducted. The working group could also specify the HRQoL scale to be used in the trial.

- Even if a large multicenter trial is not feasible, we suggest that smaller future trials evaluating the impact of rhGH in patients with CF be placebo controlled; 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.

- There is value in conducting smaller scale trials with the primary objectives of discerning the impact of rhGH on pulmonary parameters, exercise tolerance, and HRQoL. While no significant improvement in percent predicted FEV_1 or exercise tolerance was found in our Comparative Effectiveness Review, there were qualitative improvements, and future studies would allow us to determine if these were real but underpowered effects.

- For exercise tolerance and HRQoL, the Cystic Fibrosis Foundation and trialists should specify which exercise tolerance tests and HRQoL questionnaires should be used across future studies to facilitate pooling.

- As with the evaluation of benefits, future trials should prespecify the harms they will assess, and should report on their results even if they are underpowered to perform quantitative synthesis.

- Trials with treatment durations of 6 months or of 12 months or longer would be helpful in determining the adequate duration of therapy.

Observational Studies

- Future observational trials should evaluate the relationship between:
    - The absolute change in FEV_1 and final health outcomes in patients with CF.
    - Bone mineralization and final health outcomes in patients with CF.
    - IGF-I concentrations at the time of cancer occurrence in patients with CF.

Full Report

This executive summary is part of the following document: Phung OJ, Coleman CI, Baker EL, Scholle JM, Girotto JE, Makanji, SS, Chen WT, Talati R, Kluger J, Quercia R, Mather J, Giovenale S, White CM. Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis. Comparative Effectiveness Review No. 23. (Prepared by the University of Connecticut/Hartford Evidence-based Practice Center under Contract No. 290-2007-10067-1.) AHRQ Publication No. 11-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2010. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis

Key Question 1. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function, growth (height, weight, lean body mass, protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Pulmonary function					
Absolute FVC	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	1	No	No effect	Insufficient
Percent predicted FVC	Controlled	5	Yes	rhGH better than control	Low
	Single-arm	2	No	Mixed results from baseline	Insufficient
Absolute FEV_1	Controlled	4	Yes	rhGH better than control	Moderate
	Single-arm	1	No	No effect	Insufficient
Percent predicted FEV_1	Controlled	4	Yes	No effect	Moderate
	Single-arm	2	No	No effect	Insufficient
FEV_1 Z-score	Controlled	1	Yes	No effect	Insufficient
	Single-arm		No data are available		Insufficient
Anthropometrics					
Height	Controlled	3	Yes	rhGH better than control	Low
	Single-arm	1	No	Improvement from baseline	Insufficient
Height velocity	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	4	No	Improvement from baseline	Insufficient
Height Z-score	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	3	No	Improvement from baseline	Low
Height percentile	Controlled	1	No	rhGH better than control	Insufficient
	Single-arm		No data are available		NA
Weight	Controlled	5	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Improvement from baseline	Insufficient
Weight velocity	Controlled	2	Yes	rhGH better than control	Moderate
	Single-arm	3	No	No effect	Low
Weight Z-score	Controlled	4	Yes	No effect	Low
	Single-arm	1	No	Improvement from baseline	Insufficient

Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis (continued)

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Key Question 1 (continued). In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function, growth (height, weight, lean body mass, protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?					
Anthropometrics (continued)					
Weight percentile	Controlled	1	No	rhGH better than control	Insufficient
	Single-arm		No data are available		Insufficient
Body mass index	Controlled	2	Yes	rhGH better than control	Moderate
	Single-arm	1	No	No effect	Insufficient
BMI Z-score	Controlled	1	Yes	No effect	Insufficient
	Single-arm		No data are available		Insufficient
Percent IBW	Controlled	2	Yes	rhGH better than control	Low
	Single-arm		No data are available		Insufficient
Lean body mass	Controlled	8	Yes	rhGH better than control	Moderate
	Single-arm		No data are available		Insufficient
Protein markers					
Various	Controlled	2	No	Mixed results	Insufficient
	Single-arm	1	No	No effect	Insufficient
Exercise tolerance					
Various	Controlled	3	No	No effect	Insufficient
	Single-arm	1	No	No effect	Insufficient
Bone mineralization					
Bone age	Controlled	2	No	No effect	Insufficient
	Single-arm	3	No	No effect	Low
BMC	Controlled	4	Yes	rhGH better than control	Low
	Single-arm		No data are available		Insufficient
BMC Z-score	Controlled	1	No	rhGH better than control	Insufficient
	Single-arm		No data are available		Insufficient

Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis (continued)

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Key Question 1 (continued). In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function, growth (height, weight, lean body mass, protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?					
Sexual maturation					
	Controlled	7	No	rhGH better than control	Low
	Single-arm		No data are available		Insufficient
Key Question 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?					
Antibiotic usage	Controlled	3	No	rhGH better than control	Insufficient
	Single-arm		No data are available		Insufficient
Pulmonary exacerbations	Controlled	1	No	No effect	Insufficient
	Single-arm		No data are available		Insufficient
Hospitalization rate	Controlled	4	Yes	rhGH better than control	Moderate
	Single-arm		No data are available		Insufficient
HRQoL	Controlled	2	No	rhGH better than control	Insufficient
	Single-arm		No data are available		Insufficient
Bone consequences			No data are available.		Insufficient
Mortality			No data are available.		Insufficient
Key Question 3. In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?					
Mortality					
Pulmonary function	Observational	28	No	Mixed results	NA
Anthropometrics	Observational	26	No	Mixed results	NA
Protein turnover	Observational		No data are available		NA
Exercise tolerance	Observational	10	No	Mixed results	NA
Bone mineralization	Observational		No data are available		NA

Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis (continued)

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Key Question 3 (continued). In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?					
HRQoL					
Pulmonary function	Observational	14	No	Improved pulmonary function relates to improved HRQoL	NA
Anthropometrics	Observational	10	No	Mixed results	NA
Protein turnover	Observational		No data are available	No data are available	NA
Exercise tolerance	Observational	2	No	Improved exercise tolerance relates to improved HRQoL	NA
Bone mineralization	Observational		No data are available	No data are available	NA
Bone consequences					
Pulmonary function	Observational	1	No	No association found	NA
Anthropometrics	Observational	1	No	No association found	NA
Protein turnover	Observational		No data are available	No data are available	NA
Exercise tolerance	Observational		No data are available	No data are available	NA
Bone mineralization	Observational		No data are available	No data are available	NA
Key Question 4. 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	Yes	No effect	Low
	Single-arm	2	No	No effect	Low
Random BG	Controlled	3	Yes	Glucose levels remained stable	Insufficient
	Single-arm		No data are available	No data are available	Insufficient
Fasting BG	Controlled	2	Yes	Increased with rhGH compared to control	Moderate
	Single-arm	1	No	No effect	Insufficient

Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis (continued)

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Key Question 4 (continued). 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 (continued)					
Stimulated BG	Controlled	1	Yes	No effect	Insufficient
	Single-arm		No data are available		Insufficient
Postprandial BG	Controlled	1	Yes	No effect	Insufficient
	Single-arm		No data are available		Insufficient
Glucose intolerance					
	Controlled	7	No	No patients developed	Low
	Single-arm	3	No	Few patients developed	Insufficient
Diabetes					
	Controlled	7	No	No patients developed	Low
	Single-arm	1	No	One case report of diabetes	Insufficient
Injection site reactions					
	Controlled		No data are available		NA
	Single-arm	2	No	Minor discomfort and bruising reported	NA
Liver transaminases					
	Controlled		No data are available		NA
	Single-arm	2	No	Limited report of liver transaminase elevations	NA
Study withdrawals					
	Controlled	10	No	Majority of trials reported no withdrawals	NA
	Single-arm		No data are available		NA
Biomarkers					
IGF-I	Controlled	4	No	rhGH increases more than control	Insufficient
	Single-arm	2	No	Increased from baseline	Insufficient

Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis (continued)

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Key Question 4 (continued). 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.					
Biomarkers (continued)					
IGFBP-3	Controlled	1	No	rhGH increases more than control	Insufficient
	Single-arm	1	No	Increased from baseline	Insufficient
Key Question 5. What is the risk of malignancy associated with rhGH use as determined by (a) markers of cancer risk with rhGH (IGF-I increases over 100 ng/ml or IGFBP-3 decreases over 1,000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2 mg/kg/week to 0.6 mg/kg/week) for disorders such as growth hormone deficiency and idiopathic short stature?					
Cancer incidence in CF patients					
	Controlled		No data are available		Insufficient
	Single-arm	1	No	Case report shows probable relationship between rhGH and cancer	Insufficient
Cancer incidence in non-CF patients					
	Controlled		No data are available		Insufficient
	Single-arm	3	No	Insufficient data to make conclusions about rhGH effect on cancer	Low
Key Question 6. In patients with CF, how are efficacy, effectiveness, safety, or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?					
Dose	Controlled	1	No	No significant differences between dose groups in endpoints	NA
Duration	Controlled	9	Yes	1-year therapy trends toward improved efficacy vs. 6 months therapy. 1-year therapy trends toward increased glucose parameters vs. 6 months therapy.	NA
Baseline nutritional status	Controlled	1	No	There is limited evidence in patients with variable nutritional status. Efficacy exists in patients receiving enteral nutrition.	NA
Concurrent medical therapies	Controlled		No data are available		NA

Table A. Summary of results of studies of the effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis (continued)

Outcome	Type of study	Number of studies	Pooled	Conclusion	Strength of evidence
Key Question 7. In patients with CF, how do the efficacy, effectiveness, safety, or 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, lean body mass, pulmonary function, exercise tolerance, nutritional status), and/or the nature, extent, and effectiveness of prior treatment.					
Age	Controlled	6	Yes	Pubertal patients may derive greater benefit in pulmonary function, weight, and bone mineral content than prepubertal patients. Prepubertal patients may derive greater benefit in height than pubertal patients.	NA
Gender	Controlled	3	Yes[*]	Females (both prepubertal and pubertal) may experience greater benefit in height and weight than males.	NA
Baseline clinical status	Controlled	2	No	Patients with lower baseline height Z-score experienced greater height improvement than those with higher height Z-score. Higher baseline weight was correlated with greater improvement in pulmonary function.	NA
Prior treatment			No data are available		NA

Note: A1c=glycosylated hemoglobin; BG=blood glucose; BMC=bone mineral content; BMI=body mass index; CF=cystic fibrosis; FEV=forced expiratory volume in 1 second; FVC=forced vital capacity; HRQoL=health-related quality of life; %IBW=percent ideal body weight; IGF-I=insulin-like growth factor-1; IGFBP-3=insulin-like growth factor binding protein-3; NA=not assessed.

[*]Data pooled from 3 trials by Vanderwel and Hardin.