ORIGINAL ARTICLE

Prospective randomised treatment with recombinant human growth hormone in cystic fibrosis

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Aim: To evaluate the efficacy and safety of treatment with recombinant growth hormone (rGH) in patients with cystic fibrosis (CF).

Methods: Twenty patients with CF (aged 10–23 years) were randomised to age and sex matched treatment and control groups. The treatment group received daily subcutaneous injections of 1 IU/kg/wk rGH for 12 months. Pulmonary function (forced expiratory volume in one second (FEV_1) and airway resistance), exercise capacity measured with a bicycle ergometer, body composition (dual energy *x* ray absorptiometry), and weight were assessed at the beginning of the study and after 6 and 12 months.

Results: rGH treatment did not improve weight and pulmonary function, but lean body mass increased significantly in the treatment group. Exercise capacity increased in the treatment group from 143 (16) W (mean (SD)) to 164 (19) W after 12 months of rGH treatment.

Conclusion: Treatment of CF patients with rGH for one year improved the exercise capacity significantly but not pulmonary function. The improved exercise capacity needs confirmation in a larger population before such an expensive treatment is justified.

Cystic fibrosis (CF) is characterised by a progressive lung disease and malnutrition, which results in increased morbidity and mortality.[1] The progress of the treatment of CF has improved morbidity and mortality, but the impaired lung function and exercise capacity has a major impact on the patient's quality of life.[2] CF patients have a constant decrease in muscle mass which is caused by the constant wasting of lean tissue,[3] and some studies found a reduced respiratory muscle strength in CF.[4] Treatment of patients with a chronic and progressive disease with growth hormone has become very popular, especially as biosynthetic recombinant growth hormone (rGH) is readily available. Recombinant GH was administered in patients with cancer,[5] after surgery,[6 7] after burns,[8] and in patients with HIV.[9] These studies showed an improvement in body composition in adults and children.[10 11] Furthermore, in patients with HIV infection associated wasting syndrome, rGH enhanced body weight, lean body mass (LBM), and exercise capacity measured on a treadmill.[12 13] Treatment with rGH in patients with chronic obstructive pulmonary disease (COPD) resulted in a positive nitrogen balance, but exercise capacity remained unchanged.[14 15] Only a few studies have investigated the effect of rGH treatment in patients with CF. Sackey and colleagues[16] found in a small group of children a significant increase in height velocity and weight gain. Huseman and colleagues[17] studied the anabolic effect of rGH; they observed a significant improvement in linear growth and redistribution of fat and muscle tissue, but neither an increase in weight nor changes of pulmonary function could be detected. In contrast, Hardin and Sly[18] showed increased weight for height expressed in standard deviation scores (SDS) after 24 months when prepubertal patients with CF were treated with rGH.

As rGH has become an important (and abused) drug to enhance endurance and exercise capacity in athletics, it is tempting to investigate this effect in patients with LBM deficiency. These patients may benefit from improved exercise capacity. Therefore the aim of this prospective, randomised, controlled study was to assess the effect of rGH treatment during 12 months on LBM, exercise capacity, and pulmonary function of CF patients in a randomised, age and sex matched study.

METHODS

Study design

Sex and aged matched pairs of CF patients were recruited in the outpatient clinic of the University Children's Hospital in Bern, Switzerland and then randomly assigned to a treatment and control group. Both groups were studied for 12 months. Anthropometric data, body composition, pulmonary function, and exercise capacity of all patients were measured at the beginning, and after 6 and 12 months. Lean body mass and glucose tolerance were measured at the beginning of the study and after 12 months.

Patients and treatment protocol

Twenty CF patients were enrolled in the study. The diagnosis of CF was confirmed by a positive sweat test and analysis of the mutated CFTR gene (table 1). Exclusion criteria were insulin dependent diabetes mellitus, hepatic disease, evidence of portal hypertension, and patients with clinically evident congestive heart failure. The study was approved by the Ethical Committee of the University Children's Hospital, Bern, Switzerland. Written informed consent was obtained from the patients and/or their parents.

Patients in the treatment group received rGH (Saizen, Serono SA, Aubonne, Switzerland) 1 IU/kg/wk by daily subcutaneous injections for 12 months. Side effects of rGH treatment were recorded in the protocol. Treatment was continued according to our standard protocols for CF outpatients.

Abbreviations: AT, anaerobic threshold; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; DXA, dual energy *x* ray absorptiometry; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LBM, lean body mass; R_{aw}, respiratory airway resistance; rGH, recombinant growth hormone; VCO_2, carbon dioxide output; VO_{2max}, maximal oxygen consumption; W, watt

Table 1 Biometric and CF disease specific data

	Treatment group (n = 10)	Control group (n = 9)
Mean age, years (range)	15.4 (11–22)	16.8 (10–23)
Sex (M/F)	8/2	7/2
Genotype for CF		
$\Delta F_{508}/\Delta F_{508}$	3	6
ΔF_{508}/other	5	2
Other/other	2	1
Clinical score (Bernese score), mean (SD)	21.3 (2.1)	19.1 (2.3)
Chest radiograph score (Chrispin-Norman score), mean (range)	8.7 (5−15)	10.2 (6–13)
Relative underweight (%), mean (SD)	6.25 (5.1)	6.2 (5.9)
Weight for height SDS, mean (SE)	−0.69 (0.23)	−0.99 (0.21)

SDS, standard deviation score.
Relative underweight, expressed in percentage of normal range (50th centile).[24]

Measurement protocol

A glucose tolerance test (45 g/m^2/dose) was performed at the beginning of the study and after 12 months. The patients had to fast overnight; blood glucose levels were measured prior to and 120 minutes after glucose exposure.

Body composition and lean body mass were assessed at the beginning and at the end of the study (12 month) by dual energy *x* ray absorptiometry (DXA) (Hologic QDR 1000/W, Hologic Inc., Bedford, MA). A calibration phantom for soft tissue was scanned in parallel with the subjects. The software calculated the body fat percentage based on extrapolation of fatness from the ratio of soft tissue attenuation of the two *x* ray energies in pixels not containing bone. The ratio was determined for each pixel that contains a minimal amount of soft tissue (3 g/cm^2) but no significant bone (<0.2 g/cm^2). Quality control of the machine was performed daily by scanning an anthropometric phantom supplied by the manufacturer. The coefficient of variation for repeated measurements with repositioning of the subjects (n = 4) was 0.28% for lean body mass.

Pulmonary function was measured with whole body plethysmography and spirometry (Master Screen, E. Jaeger, Würzburg, Germany). Functional vital capacity (FVC), forced expiratory volume in one second (FEV_1), and airway resistance (R_{aw}) were recorded. Results were expressed as percentages of age, sex, and height predicted normal values.[19–21]

Exercise capacity. Maximal workload (W_{max}) and maximal oxygen consumption (VO_{2max}) were measured with a cardiopulmonary exercise testing unit (Vmax 229, Sensormedics Corp., Anaheim, CA) while the patient was exercising on an electronically braked bicycle (Ergometrics 900, Sensormedics Corp., Anaheim, CA). Transcutaneous oxygen saturation and the electrocardiogram were monitored during the exercise. The first workload of the protocol was defined with 1 W/kg for the individual patient. The work load was then increased with constant increments of 10 W. The time intervals were continuously decreased to keep the product of work and time interval at each level constant (modified Conconi protocol).[21 22] A three minute warm-up period preceded the exercise test. The exercise test was stopped when the patient indicated subjective exhaustion. Oxygen consumption (VO_2), carbon dioxide output (VCO_2), and the respiratory quotient (RQ) were recorded breath by breath. VO_{2max} expressed in ml/kg/min was determined at the end of the test, and VO_{2max} at anaerobic threshold (AT) when RQ was 1.0.

The Chrispin-Norman score[23] expresses the pulmonary involvement of CF based on a scoring of changes found in the chest radiograph, and the Bernese score[19] measures the multiorgan dysfunction of CF. Both scores were assessed at the beginning and after 6 and 12 months. Body weight was expressed with relative underweight (%) and with standard deviation scores (SDS) using reference values.[24] All patients were examined by the same physician (RvH).

There was one drop out in the control group after six months (evaluation for lung transplantation).

Statistical analysis

We wanted to detect a clinically significant difference (±20%) between groups (control and treatment group), assuming a mean (SD) working capacity of 2–3 W/kg in one group and a correlation between repeated measurements within an individual of 0.7. Using ANOVA with repeated measurements for $\alpha = 0.05$ (two sided) and a power of 80%, including three measurements, the necessary sample size was eight patients per group. The baseline study parameters between the two groups were compared using a paired *t* test. A p value <0.05 was considered significant. Data are expressed as means (SE).

RESULTS

In the control group there was one drop out because the patient was evaluated for lung transplantation.

Table 1 lists the biometric data of the two study groups. At study entry body weight, age, and disease severity using the clinical (Bernese) and the chest radiograph score were similar in both groups. Additionally no differences were found for baseline pulmonary function (FEV_1, FVC, R_{aw}) and baseline exercise capacity (VO_{2max} and W_{max}). There was no difference in relative underweight using normal reference values from a Swiss population.[24]

Follow up for 12 months showed no change in body weight and pulmonary function of the CF patients in the treatment and control groups (table 2). In the treatment group LBM increased significantly after 12 months, whereas in the control group no significant change in LBM was found.

W_{max} increased significantly in the treatment group ($p<0.05$) from 143 (16) Watts to 164 (19) Watts, but not in the control group (147 (14) and 136 (19) Watts, respectively) after the 12 month study period. VO_{2max} remained unchanged in the treatment group (40.7 (2.7) and 38.2 (2.1) ml/kg/min, respectively), but decreased significantly in the control group after 12 months ($p = 0.003$) from 44.1.0 (3.5) to 35.5 (2.5) ml/kg/min. VO_{2max} corrected for LBM decreased significantly after 12 months in the control group but not in the treatment group (table 2). VO_{2max} at AT decreased significantly in the treatment but not in the control group after 12 months. None of the investigated CF patients showed a desaturation of haemoglobin during the exercise test.

The fasting glucose level at the beginning of the study and the response to the oral glucose load were similar in both groups. The mean fasting glucose level in the control group was 5.0 (0.5) mmol/l, and after the glucose challenge 8.1 (1.9) mmol/l. In the treatment group the mean fasting glucose was 5.3 (0.5) mmol/l, and 8.0 (2.8) mmol/l after the glucose challenge. After 12 months the glucose tolerance of patients in the treatment group remained unchanged; mean fasting glucose was 5.7 (0.4) mmol/l, and after the oral glucose load 6.6 (0.4) mmol/l. Long term treatment with growth hormone may increase mean blood glucose levels. Such a change could not be documented by measuring glycated haemoglobin values ($\Delta HbA1_c$) at the beginning and at the end of the study (0.38 (0.58)% and 0.24 (0.40)%,

Table 2 Results of the 12 month study period

	Treatment group		Control group	
	At 6 months	At 12 months	At 6 months	At 12 months
Weight (SDS)	−0.11 (0.094)	−0.016 (0.10)	−0.0056 (0.13)	−0.026 (0.13)
LBM (kg)		4.1 (0.75)*		1.6 (0.67)
FEV_1 (%)	−5.6 (3.7)	0.8 (3.9)	−3.4 (3.6)	−0.4 (4.1)
FVC (%)	−2.8 (3.2)	3.6 (3.4)	−4.2 (3.0)	0.4 (2.5)
R_{aw} (%)	15.1 (19.9)	−20.1 (12.6)	−15.3 (22.4)	−30.6 (27.1)
W_{max} (Watt)	1.7 (7.3)	21.0 (7.3)*	−21.4 (9.2)	−10.9 (12.3)
$VO_{2\ max}$ (ml/kg/min)	−1.5 (1.6)	−2.5 (2.3)	−5.9 (7.0)	−8.6 (1.7)*
$VO_{2\ max}$/LBM (ml/kg/min)		−2.5 (2.3)		−8.6 (1.7)*
$VO_{2\ max}$ at AT (ml/kg/min)	−2.5 (1.5)	−4.1 (1.7)*	−4.0 (4.5)	−5.4 (2.6)

Changes from baseline at 6 and 12 months are given in the table. Weight is expressed in standard deviation scores (SDS).
LBM, lean body mass; FEV_1, forced expired volume in one second; FVC, forced vital capacity; R_{aw}, airway resistance in percent predicted; W_{max}, maximal working capacity; $VO_{2\ max}$, maximal oxygen consumption.
*Significant change from baseline to 12 months ($p<0.05$).

respectively). No other side effects of rGH treatment were recorded.

DISCUSSION

In the present study we hypothesised that treatment with rGH in patients with CF improves pulmonary function, exercise capacity, and LBM. Such an improvement would have been expected based on previous experience with rGH treatment in other progressive and catabolic disease such as cancer, COPD, and HIV.[5 9 14 15] We could show a significant increase of exercise capacity in the treatment group after a one year treatment with rGH. LBM increased accordingly but did not reach statistical significance, whereas pulmonary function in the treatment group remained unchanged. These parameters have been shown to be good clinical indicators for quality of life, not only in GH deficiency but also in subjects with normal GH secretion.[25–27] Despite the improved exercise tolerance found in the treatment group, the results of our study need to be interpreted cautiously and we question the clinical relevance of these results to support the relatively expensive treatment with rGH.

The major action of GH is to stimulate protein synthesis. GH has furthermore been shown to have a very important role in regulating body composition in adult humans and also in other species. In cattle for instance, GH is known as a ''partitioning agent''—it specifically diverts calories in food towards protein synthesis and away from fat synthesis. On the other hand, GH deficient (GHD) adults have reduced lean body mass and increased fat mass, particularly central abdominal fat mass.[27] Recombinant GH given in physiological ''replacement'' doses to adults with GHD results in remarkable changes in body composition with, on average, a 5 kg increase in lean body mass within the first month[26] and a comparable loss of 5 kg of fat. The fat loss is particularly from the intra-abdominal region where fat accumulates in the GHD state. In parallel with these changes in body composition, the subnormal exercise performance and strength of adults with GHD are returned to normal.[26–30]

Although there are no proper scientific studies proving GH to be performance enhancing in normal subjects, few doubt this ability. VO_{2max} is determined by several factors: alveolar minute volume, diffusion capacity of the lungs, cardiac output and cardiac function, haemoglobin level, and the number and quality of muscle fibres involved in the exercise. VO_{2max} is an estimate of endurance and may be improved by regular exercise. W_{max} may be improved by increased muscle mass.[31] The CF patients in the treatment group showed a significant improved W_{max} and unchanged VO_{2max}, whereas CF patients in the control group had no improvement in W_{max} and a significant decrease in VO_{2max} ($p<0.003$) after 12 months. During the natural course of CF disease, VO_{2max} and W_{max} decrease.[2] Therefore any improvement of W_{max} or stable VO_{2max} during 12 months can be interpreted as a positive effect of the rGH treatment. The primary intention of this study was to show the effect of rGH treatment on exercise capacity. To eliminate an important confounding factor, patients in the study were instructed not to change their exercise habits. However, it has been shown that that rGH improves VO_{2max} only in combination with regular exercise,[27] but this ergogenic effect of systemic administration of rGH by athletes and bodybuilders (healthy subjects) remains unproven.[31] We may therefore speculate that patients in the treatment group would benefit more from rGH treatment and additional exercise than a control group. Recombinant GH treatment may increase the number of muscle fibres, but not necessarily the ones rich in mitochondria. A study design with a well defined exercise protocol might have resulted in an improved exercise capacity in the treatment group. Despite the significant change of W_{max} found in our study, the results may not be clinically relevant. A longer study period would be necessary; furthermore, our data only relate to a small group of CF patients.

The LBM of the patients in the treatment group increased significantly. This finding may partly explain the improved exercise capacity. Previous studies in patients with CF suggested such an anabolic effect of GH treatment.[16 17] Huseman and colleagues[17] analysed the anabolic effect of rGH treatment and found a less negative net nitrogen balance, an increase in protein, and a decrease in fat stores, but no weight gain or improvement in pulmonary function after rGH treatment. Huseman administered rGH for three days per week but the absolute doses used were comparable to ours.

The pulmonary function of the CF patients in the present study remained unchanged in both groups during the 12 months follow up. In previous studies in patients with chronic lung disease it has been shown that rGH treatment did not improve pulmonary function.[14–17] Lung disease in CF patients is characterised by a thick mucus layer and an inflammatory process activated by bacterial colonisation of the bronchial surface. The inflammatory process leads to alveolar destruction and destabilisation of the airways, and, once the inflammatory process has stopped, to interstitial fibrosis. rGH as an anabolic hormone has not been shown yet to have any positive effect on lung inflammation or repair and thus will not improve pulmonary function of CF patients.

The adverse effects of CF disease on growth and nutrition have been recorded since it was first described.[1 32] Even the body composition of CF infants without any symptoms is deficient; the degree of underweight correlates inversely with survival[33] and has a major impact on the course of pulmonary disease. Therefore the latest management of CF has focused on nutritional support, and advances in pulmonary and antibiotic therapy have improved lung function and longevity. This form of care is able to increase the actual wellbeing and quality of life but only can postpone its inevitable decline. Our data, however, do not suggest that rGH treatment improves quality of life, although a longer study period may show a long term benefit of rGH treatment on exercise capacity and LBM.

Conclusion

Recombinant GH treatment improved exercise capacity and LBM in patients with CF but pulmonary function remained unchanged after 12 months of follow up. The moderately improved exercise capacity found in this study does not yet justify such an expensive treatment. We may speculate that in a larger cohort of CF patients GH treatment in addition to an exercise programme may improve exercise tolerance and hence quality of life. Until such data are available, quality of life in patients with cystic fibrosis should be improved with optimal clinical management and encouragement to keep up with some form of endurance training.

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