Recombinant Human Growth Hormone Treatment for Dilated Cardiomyopathy in Children

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ABSTRACT. Objective. Dilated cardiomyopathy (DCM) is one of the most common causes of heart failure among children and is often progressive despite maximal medical therapy. Heart failure is characterized by a number of neurohormonal abnormalities, including derangements in the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) signaling axis. Decreased serum levels of GH, which acts on cardiac myocytes primarily through IGF-1, are associated with impaired myocardial growth and function, which can be improved with restoration of GH/IGF-1 homeostasis. In animal models and among human adults with heart failure attributable to DCM, treatment with GH results in acquisition of left ventricular (LV) mass and improved LV function, through a combination of mechanisms. We undertook this study to determine the effects of recombinant human GH on LV function and mass among children with stable LV dysfunction attributable to DCM.

Methods. We performed a prospective, single-center, randomized, partially blinded, crossover trial among children 1 to 19 years of age with DCM and cardiac dysfunction of ≥6-month duration. After enrollment, patients were randomly assigned to receive treatment for 6 months with either conventional therapy (determined by the patient’s primary cardiologist) plus recombinant human GH (0.025–0.04 mg/kg per day), administered as daily subcutaneous injections, or conventional therapy alone. Patients GH then were crossed over to the other treatment strategy for 6 months. The primary outcome measure was change in LV shortening fraction (SF). Other echocardiographic indices of LV function, somatic growth, and somatotropic/thyroid hormone levels were also monitored.

Results. Only 8 of an intended 15 patients were enrolled, because of a combination of factors. Two patients withdrew during the study as a result of declining LV function requiring transplantation. LV SF did not change significantly during GH treatment, although both LV SF and LV SF z score were higher 6 months after cessation of GH treatment than at baseline. LV ejection fraction increased during GH therapy to a degree that approached significance. Height and weight percentiles for age increased significantly during GH therapy and remained higher 6 months after treatment. Annualized height velocity during GH treatment (13.7 ± 3.3 cm/year, >97th percentile for all patients) was significantly higher than that after GH discontinuation (3.2 ± 3.5 cm/year). Serum levels of IGF-1 and IGF-binding protein-3 were significantly higher after 6 months of GH treatment and 6 months after discontinuation of GH treatment than at baseline. There were no adverse events related to GH treatment.

Discussion. In this prospective, single-center, randomized, partially blinded, crossover trial, recombinant human GH was administered to 8 pediatric patients with stable chronic heart failure secondary to DCM. Because of unanticipated difficulty enrolling eligible patients, the study was underpowered to detect changes in our primary outcome measure of the magnitude we projected. Nevertheless, we did observe several notable cardiovascular effects of GH treatment, including a trend toward improved LV ejection fraction during the course of GH treatment and significantly improved LV SF, SF z score, and LV end systolic stress z score 6 months after discontinuation of GH treatment (relative to baseline values). Given the fact that levels of IGF-1, the primary myocardial effector of GH signaling, remained significantly higher 6 months after GH treatment than at baseline, the improvement in LV functional indices 6 months after discontinuation of therapy may represent progression or perpetuation of a GH treatment effect. In addition to its cardiovascular effects, GH therapy was associated with significant acceleration of somatic growth. The benefits of GH were not associated with significant attributable side effects, although 2 patients developed progressive LV dysfunction during the study and underwent cardiac transplantation.

ABBREVIATIONS. DCM, dilated cardiomyopathy; GH, growth hormone; ED, end diastolic; EF, ejection fraction; ESS, end systolic stress; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein-3; LV, left ventricular; SF, shortening fraction; TBGI, thyroxine-binding globulin index; T₃, triiodothyronine; T₄, thyroxine.

Dilated cardiomyopathy (DCM) is uncommon among children but constitutes the principal indication for cardiac transplantation in childhood.1 Cardiac dysfunction among children with DCM is often progressive despite maximal anticongestive therapy, with significant morbidity and mortality.2,3 Although the outcomes of cardiac trans-
plantation among children are improving steadily, there is a paucity of donor organs and an increasing number of listed patients, as well as persistent concerns regarding intermediate and long-term morbidity and death. Therefore, it is imperative to develop novel strategies for optimizing nontransplant treatment of children with heart failure attributable to DCM.

Heart failure is characterized by a number of neurohormonal perturbations, including abnormalities in the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) signaling axis. Abnormal serum levels of GH, which acts on cardiac myocytes primarily through IGF-1, are associated with abnormalities of myocardial growth and function that can be ameliorated with restoration of GH/IGF-1 homeostasis, as demonstrated by experience with patients with deficiency or hypersecretion of GH. Studies in animal models of heart failure have demonstrated salutary effects of exogenous GH, including increased left ventricular (LV) mass, improved LV function, and preservation of myocyte Ca\(^{2+}\) homeostasis and β-adrenoceptor responsiveness. GH/IGF-1 signaling also stimulates myosin phenoconversion, with a shift toward more energy-efficient isoforms, as well as sympathetic deactivation, inhibition of inflammatory cytokine generation and apoptosis, and attenuation of the local and systemic renin-angiotensin systems. Fazio et al suggested that GH therapy may improve cardiac function among adults with DCM, although data from other human studies are equivocal. On the basis of the importance of the GH/IGF-1 axis in the maintenance of normal myocardial function and data from experimental models and adults with heart failure, we hypothesized that GH might provide a pharmacologic means of improving LV energetics and normalizing the neurohormonal milieu, thus optimizing cardiac function, among children with DCM. To determine the efficacy and safety of GH in the treatment of pediatric DCM, we undertook a prospective, single-center, randomized, partially blinded, crossover trial among subjects 1 to 19 years of age with DCM and cardiac dysfunction of ≥6-month duration.

METHODS

Subjects

Patients 1 to 19 years of age with DCM and echocardiographic evidence of sustained cardiac dysfunction for at least 6 months were identified by searching departmental databases and announcing the study to pediatric cardiologists in New England and New York State. DCM was defined according to the following echocardiographic parameters, which are based on normative data derived at our institution: 1) LV end diastolic (ED) dimension ≥2 SD above the mean for body surface area (± score ≥ 2) and 2) LV shortening fraction (SF) or ejection fraction (EF) ≤3 SD below the mean for age (± score ≤ −3). Patients meeting any of the following criteria were excluded: 1) associated cardiovascular anomalies, including aortic coarctation, coronary artery anomalies, and hemodynamically significant LV outflow tract obstruction; 2) prior cardiac surgery; 3) a known cause of DCM (eg, doxorubicin toxicity, metabolic disorders, or muscular dystrophies); 4) associated untreated endocrine abnormalities, including diabetes mellitus and hypothyroidism; 5) Turner’s syndrome; 6) systemic hypertension; or 7) symptoms of heart failure at rest. With the permission of the primary cardiologist, an attempt was made to contact the parents of qualifying patients. Written informed consent for study participation was obtained for all patients enrolled, in accordance with a protocol approved by the institutional review board of Children’s Hospital (Boston, MA).

Treatment Arms

After enrollment, patients were randomly assigned to receive treatment for 6 months with either conventional therapy plus recombinant human GH (Humatrope; Eli Lilly and Co, Indianapolis, IN), administered as daily subcutaneous injections (group 1), or conventional therapy alone (group 2). Patients were then crossed over to the other treatment strategy for 6 months. For pubertal patients, the dose of GH was 0.04 mg/kg per day; for pubertal patients, GH was initiated at a dose of 0.025 mg/kg per day and then adjusted as necessary to maintain serum IGF-1 levels of 250 to 500 ng/mL. Group 2 patients were monitored for an additional 6 months after discontinuation of GH therapy. Conventional therapy was administered to each patient according to the preference of his or her primary cardiologist.

Evaluation of Outcome Measures

Echocardiographic Measures

Echocardiographic evaluation, consisting of a complete, 2-dimensional, cross-sectional echocardiogram and Doppler evaluation including M-mode-derived LV mass and end systolic stress (ESS)-velocity analyses, was performed at the time of study entry and at the 6-month, 12-month, and (for group 2 only) 18-month time points. LV volumes were calculated with the biplane Simpson’s rule algorithm. z scores (number of SDs from the expected population mean for age or body surface area) were calculated for study patients on the basis of measurements among normal subjects 1 to 19 years of age who were studied in our echocardiography laboratory. Each echocardiographic study was analyzed by an attending echocardiographer (S.D.C.), who was blinded with respect to patient and treatment phase.

Somatom Growth Indices and Bone Age Analysis

Height and weight were measured at the time of study entry and at the 6-month, 12-month, and (for group 2 only) 18-month time points. Percentiles for age were estimated from standard population-based nomograms, and body surface area was calculated according to the method described by Haycock et al. Bone age was estimated with standard methods from radiographs of the patient’s left wrist obtained at the time of initiation of GH therapy and 6 months after discontinuation of GH, by an attending pediatric radiologist who was blinded with respect to treatment phase. The bone age index was calculated as the ratio of bone age to chronological age.

Endocrine Laboratory Studies

Serum levels of GH, IGF-1, IGF-binding protein-3 (IGFBP-3), thyroid-stimulating hormone, total thyroxine (T4), total triiodothyronine (T3), thyroxine-binding globulin index (TBGI), glucose, and hemoglobin Alc were measured with standard assays at the time of study entry and at the 6-month, 12-month, and (for group 2 only) 18-month time points. Thyroid function studies, glucose levels, and hemoglobin Alc levels were monitored because of the known effects of GH on the thyroid axis and glucose tolerance.

Adverse Event Monitoring

Adverse events were recorded and classified according to their relationship to GH therapy (ie, not related, probably not related, possibly related, or probably related) and severity (ie, not serious, moderately serious, or serious).

Data Analyses

Data are presented as median and range or mean ± SD. Paired t test analyses were used to assess rates of change of continuous outcome measures. To determine whether changes in outcome measures were attributable to trends with time, between-subject comparisons of rates of change of outcome measures during the first and second 6-month periods were performed with unpaired t test analyses. Generalized estimating equations, which adjust for the effects of repeated observations, were used to compare mean

values at the measured times with the baseline mean values, to assess changes in outcome measures during GH therapy. To assess carryover or deterioration of treatment effects beyond the period of GH administration, mean values measured 6 months after discontinuation of GH were compared with mean values at baseline. The primary outcome measure was change in LV SF. On the basis of power calculations with a 2-sided significance level of .05, enrollment of 15 subjects was estimated to provide 82% power to detect an absolute change of 3% in LV SF (eg, from 10% to 13%) and 99% power to detect an absolute change of 5% in LV SF.

RESULTS

Patients

With review of departmental databases, 119 patients between the ages of 1 and 19 years with DCM were identified. Of these 119 patients, 96 were ineligible because of death (n = 7), cardiac transplantation (n = 8), improvement in LV function (n = 48), form of cardiomyopathy other than DCM (n = 15), metabolic disease (n = 6), hypertensive cardiomyopathy (n = 3), other known cause of DCM (n = 4), congenital heart disease and/or prior history of cardiac surgery (n = 3), or symptoms of heart failure at rest (n = 2). Of the 23 eligible patients, 5 were living overseas and 3 could not be located. The remaining 15 patients and their parents were invited to participate in the study, but 7 (47%) declined. Therefore, 8 patients were ultimately enrolled and randomized between November 1999 and October 2000. Baseline demographic and clinical data for these 8 study patients are summarized in Table 1. Seven of the patients were prepubertal at the time of study entry and throughout the study period and accordingly received a GH dose of 0.04 mg/kg per day; 1 patient was pubertal at the time of study entry and continued to receive the starting GH dose of 0.025 mg/kg per day, without adjustment, for the duration of the treatment phase.

TABLE 1. Baseline Demographic and Clinical Data

| Age, y, median (range) | 3.0 (1.0–13.8) |
| Time from DCM diagnosis to enrollment, y, median (range) | 2.1 (0.8–5.0) |
| Gender, no. | | |
| Male | 3 |
| Female | 5 |
| Ethnicity, no. | | |
| White | 5 |
| Hispanic | 2 |
| African American | 1 |
| New York Heart Association clinical status, no. | | |
| Class I | 4 |
| Class II | 4 |
| DCM type, no. | | |
| Familial | 2 |
| Idiopathic | 6 |
| Additional cardiovascular medications, no. | | |
| ACE inhibitors | 8 |
| Digoxin | 7 |
| Furosemide | 4 |
| Spironolactone | 3 |
| Aspirin | 3 |
| ß-Adrenergic receptor antagonists | 2 |
| Blood pressure, mm Hg, median (range) | | |
| Systolic | 89 (72–100) |
| Diastolic | 49 (37–58) |

ACE indicates angiotensin-converting enzyme.

Echocardiographic Measures

Echocardiographic measures are summarized in Table 2. LV SF, the primary outcome measure, did not change significantly during the course of GH treatment, although both LV SF and LV SF z score were significantly higher 6 months after discontinuation of GH, compared with baseline (P = .01 and P = .004, respectively). Similarly, LV EF increased during GH therapy to a degree that approached statistical significance (P = .055). Although LV mass z score increased for 5 of 7 patients during GH treatment, the change in LV mass z score relative to baseline was not statistically significant. LV ESS z score tended to be lower 6 months after discontinuation of GH (P = .052). LV ED volume z score was significantly larger after 6 months of GH treatment, compared with baseline (P = .002).

Somatic Growth Indices and Bone Age Analysis

Somatic growth indices are summarized in Table 3. During GH treatment, height percentile for age increased by a median of 23.7 percentile points (range: 4.7–29.1 percentile points) (Fig 1). During the 6 months after discontinuation of GH treatment, height percentile for age decreased for 4 of the 6 patients with available data, by a median of −12.1 percentile points (range: −21.2 to 21.0 percentile points). The annualized height velocity during GH treatment was 13.7 ± 3.3 cm/year, which was well above the 97th percentile for age and gender during this period.27 During the 6 months after discontinuation of GH treatment, in contrast, the annualized height velocity was 3.2 ± 3.5 cm/year. Weight percentile for age also increased substantially during GH treatment and plateaued thereafter. Bone age increased in accordance with chronological age.

Endocrine Laboratory Studies

Baseline laboratory results are summarized in Table 4. All baseline laboratory values were normal, except for a low IGFBP-3 level for 1 patient, high total T3 levels for 3 patients, and a high total T4 level for 1 patient. All abnormal levels normalized after GH treatment or discontinuation of GH. IGF-1 and IGFBP-3 levels increased during the period of GH administration for all patients and then decreased, stabilized, or increased slightly after discontinuation of GH (Figs 2 and 3). After 6 months of GH treatment and 6 months after discontinuation of GH treatment, serum IGF-1 (P = .006 and P = .02, respectively) and IGFBP-3 (P = .03 and P = .007, respectively) levels were significantly higher than at baseline. For 1 patient, IGFBP-3 levels increased above the upper limit of normal for age during GH treatment. Total T3 levels were significantly lower 6 months after discontinuation of GH than at baseline (P = .02), and TBGI levels were higher (P = .02). GH treatment did not cause glucose intolerance, inasmuch as blood glucose and hemoglobin A1c levels were normal at entry and for the duration of the study.
Values at this time point may appear relatively higher than at earlier time points in part because of withdrawal of the smallest patient,

Data are presented as median (range) and mean

TABLE 3.

Somatic Growth Data

Values closer to 1 indicate a more spherical ventricle, as the short-axis LV ED dimension approaches the long-axis LV ED dimension.

TABLE 2. Echocardiographic Data

Data are presented as median (range) and mean ± SD.

* Changes reflect differences between baseline measurements and measurements made at the end of the 6-month GH treatment period; P values refer to comparison with baseline measurements.

† Changes reflect differences between baseline measurements and measurements made 6 months after discontinuation of GH treatment; P values refer to comparison with baseline measurements.

‡ Values closer to 1 indicate a more spherical ventricle, as the short-axis LV ED dimension approaches the long-axis LV ED dimension.

Adverse Events

There were no deaths during the study period. Two patients in group 2 developed progressive heart failure and underwent cardiac transplantation, 1 just after starting GH treatment and the other after completing 6 months of GH treatment, in the context of a viral illness. One other patient reported possible side effects, which were considered not serious and probably not related to GH therapy, including headache, arthralgia, chest pain, and axillary swelling.
DISCUSSION

In this prospective, single-center, randomized, partially blinded, crossover trial, recombinant human GH was administered to 8 pediatric patients with stable chronic heart failure secondary to DCM. Because of unforeseen difficulty enrolling eligible patients, the study was underpowered to detect changes in our primary outcome measure of the magnitude that we anticipated. Nevertheless, we did observe several notable cardiovascular effects of GH treatment, including a trend toward improved LV EF during the course of GH treatment and significantly improved LV SF, SFz score, and ESSz score 6 months after discontinuation of GH treatment (relative to baseline values). The latter findings may represent progression or perpetuation of a GH treatment effect, particularly in light of the fact that levels of IGF-1, the primary myocardial effector of GH signaling, remained significantly higher 6 months after GH treatment, compared with baseline. In addition, GH therapy was associated with impressive somatic growth. The beneficial effects of GH were not associated with significant attributable side effects, although 2 patients developed progressive LV dysfunction during the study and underwent cardiac transplantation.

GH/IGF-1 Axis in Cardiac Failure

The rationale for administration of GH among children with heart failure attributable to DCM is based on the emerging understanding of the myocardial effects of GH and IGF-1, its primary effector in the cardiovascular system, which have been studied in a variety of experimental and clinical investigations. GH is thought to exert most of its effects on myocardial growth and function via GH receptor binding and JAK/STAT-mediated transcription of IGF-1, which in turn acts on cardiac myocytes through several different intracellular signaling pathways to alter Ca2+ trafficking, regulate expression of contractile and cytoskeletal proteins, and modify the activation of intrinsic neurohormonal networks.5,16,28–30 Patients with heart failure exhibit a number of abnormalities in the GH/IGF-1 axis, including decreased serum GH and IGF-1 levels.4,31 Decreased serum IGF-1 levels among individuals with DCM may be attributable to both decreased GH secretion in response to GH-releasing hormone and peripheral GH resistance.32,33

Potential Cardioprotective Mechanisms of GH

There are several potential mechanisms by which GH therapy may ameliorate cardiac dysfunction among patients with DCM, most of which are mediated through induction of IGF-1. GH/IGF-1 signaling augments the force-generating machinery of myocytes by down-regulating cytoskeletal proteins, thus facilitating myofibril assembly and growth, and up-regulating certain contractile proteins.13,28 Expansion of the contractile apparatus causes myocyte hypertrophy, which leads to increased wall thickness and consequent attenuation of LV wall stress (assuming that wall thickness increases more than the chamber radius) and thus myocardial oxygen consumption. Indeed, we observed decreased wall stress and fiber stress in response to GH releasing hormone and peripheral GH resistance.

Table 4. Baseline Laboratory Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IGF-1, ng/mL</td>
<td>83 (30–164)</td>
</tr>
<tr>
<td>Serum IGFBP-3, mg/L</td>
<td>2.8 (1.0–5.3)</td>
</tr>
<tr>
<td>Serum TSH, μIU/mL</td>
<td>1.74 (0.69–2.68)</td>
</tr>
<tr>
<td>Serum total T₃, ng/dL</td>
<td>159 (146–188)</td>
</tr>
<tr>
<td>Serum total T₄, ng/dL</td>
<td>9.0 (6.5–13.6)</td>
</tr>
<tr>
<td>Serum TBGI, ratio</td>
<td>0.92 (0.88–1.14)</td>
</tr>
<tr>
<td>Serum hemoglobin Alc, %</td>
<td>5.2 (4.4–5.7)</td>
</tr>
</tbody>
</table>

Data are presented as median (range). TSH indicates thyroid-stimulating hormone.

Fig 2. Serum levels of IGF-1 for each patient 6 months before the initiation of GH treatment (group 2 only), at the initiation of GH treatment, at the cessation of GH treatment, and 6 months after the cessation of GH treatment. Curves for patients in groups 1 and 2 are staggered to overlap the periods during GH treatment and after cessation of GH treatment. Group 1 and group 2 patients are indicated by solid and open symbols, respectively. Mean ± SD changes in IGF-1 levels during the 6-month periods before (group 2 only, n = 3), during (n = 7), and after (n = 6) GH treatment are also indicated.
Effects of GH in Human Cardiac Failure

Studies examining the effects of exogenous GH among adults with DCM have yielded equivocal findings. With a series of 7 patients with DCM, Fazio et al observed significant improvement in most measures of cardiac geometry and systolic function in response to GH therapy. Other investigators, however, noted only increased LV mass in response to GH, without significant changes in cardiac function or exercise capacity. Findings among adults with cardiac failure attributable to other causes, primarily myocardial ischemia, are similarly equivocal. In several of those studies, increased LV mass was correlated with the magnitude of elevation of IGF-1 levels after initiation of GH treatment, whereas others found that patients with low baseline IGF-1 levels were less likely to benefit from GH. These findings are consistent with the results of a study in which direct administration of IGF-1 improved LV function, and they suggest that GH therapy among patients with cardiac failure may lead to increased LV mass and improved LV function to the extent that serum IGF-1 levels are augmented. Patients with heart failure who manifest a blunted IGF-1 response to exogenous GH, presumably because of peripheral GH resistance, are less likely to benefit from GH treatment.

Cardiovascular Effects of GH Among Children

Although case reports have suggested that GH may be of benefit for children with DCM, no systematic studies had been performed among pediatric patients with heart failure before this investigation. However, limited data on the effects of exogenous GH on the myocardium of children without GH deficiency can be derived from studies of children with constitutional short stature, which found increased LV wall thickness and mass commensurate with somatic growth after GH therapy, with no adverse effects on cardiac function.

Somatic Growth

Among non-GH-deficient patients receiving GH because of idiopathic short stature, GH treatment leads to accelerated height velocity without markedly altering ultimate height. In our small population of children with chronic heart failure attributable to DCM, GH therapy also resulted in significantly increased somatic growth, which did not continue beyond the cessation of GH treatment. These findings raise the possibility that GH treatment of chronic heart failure among children may also aid somatic growth, which is frequently impaired among children with heart failure.

Limitations of the Study

There are several important limitations of this study, most significantly the small number of patients. Our intention was to enroll 15 subjects, but only 23 of 119 patients with DCM were eligible and only 8 of the 23 eligible patients were enrolled, in part because of a high refusal rate, which was based primarily on patient or parental discomfort with administration of daily subcutaneous injections, the major drawback of GH therapy. The low enrollment rate limits the statistical power of our study. It also highlights one of the important difficulties of conducting controlled studies with an invasive component among pediatric patients, as well as the rarity of stable chronic heart failure attributable to DCM among children. Another limitation of the study was its non-placebo-controlled design, which was chosen to avoid administration of subcutaneous placebo injections among pediatric patients. Because of this design, patients and their primary physicians were not blinded with respect to treatment phase, although outcome variables were assessed by individuals who were blinded with respect to patient and treatment phase.

Fig 3. Serum levels of IGFBP-3 for each patient 6 months before the initiation of GH treatment (group 2 only), at the initiation of GH treatment, at the cessation of GH treatment, and 6 months after the cessation of GH treatment. Curves for patients in groups 1 and 2 are staggered to overlap the periods during GH treatment and after cessation of GH treatment. Group 1 and group 2 patients are indicated by solid and open symbols, respectively. Mean ± SD changes in IGFBP-3 levels during the 6-month periods before (group 2 only, n = 3), during (n = 7), and after (n = 6) GH treatment are also indicated.

CONCLUSIONS

Six months of daily GH treatment among children with DCM and stable cardiac dysfunction results in significantly increased somatic growth and seems to have a salutary effect on LV systolic function, although difficulty enrolling patients and a consequently underpowered study hinder the interpretation of these findings. Future studies on alterations of GH/IGF-1 signaling among children with heart failure may help elucidate the indications, both cardiac and neurohormonal, for which GH may be of benefit among children with heart disease.

ACKNOWLEDGMENTS

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