Growth hormone treatment in children with rheumatic disease, corticoid induced growth retardation and osteopenia

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Abstract

Aims: In children with severe rheumatic disease (RD) treatment with corticosteroids (CS) is frequently needed and growth retardation and osteopenia may develop. A beneficial effect of human growth hormone (hGH) has been reported but mostly in trials without a control group. The aim of this project is to study the effect of hGH on growth, bone mineral density (BMD) and body composition, taking the disease activity and CS-use into account.

Methods: A randomised controlled trial on 17 prepubertal RD-patients with growth retardation and/or decreased BMD. The hGH-group (10 children) received treatment with hGH 4 IU/m2/day (~ 0.045 mg/kg/day) during two years. The controls (7 children) received no GH treatment.

Results: During the two-year study period the disease activity, use of CS and methotrexate (MTX) did not differ between the groups. There was a significant mean increase in height standard deviation score (HSDS) in the hGH-group (0.42 ± 0.16 SDS (p = 0.03)) and a non-significant decrease in the controls (-0.18 ± 0.11SDS) (difference between groups p= 0.02). Change in BMD did not differ significantly between the groups, although the increase in BMD for lumbar spine within the hGH-group was significant. Lean body mass improved significantly in the hGH-group compared to control (0.64 ± 0.19 SDS versus -0.20 ± 0.17 SDS (p<0,01)), while the decrease in percentage fat was not significant.

Conclusions: A significant effect of hGH on growth and lean body mass was seen, but a longer duration of treatment might be necessary to evaluate the effect of hGH on BMD.
Introduction

Rheumatic disease (RD) in childhood is a collective term for several chronic diseases that have an inflammatory origin and are usually associated with arthritis. Initial treatment consists of nonsteroidal anti-inflammatory drugs (NSAID's) in combination with corticosteroids (CS), sulfasalazine, methotrexate (MTX) and recently TNFα blocking agents (“biologicals”, like etanercept).

Of these medications only MTX and prednisone have an effect on growth and bone mineral density [1]. Negative side effects of long-term daily administration of especially CS are a decline of growth velocity and osteoporosis [2]. Diminished physical activity associated with arthritis negatively influences weight bearing and movement, which both play a role in the bone turnover [3]. Moreover chronic inflammation inhibits the GH-IGF-I axis resulting in a decrease in bone mineral density (BMD) and growth retardation [4] [5] [6]. In spite of the development of new treatments and all efforts to avoid long-term therapy with (high dose of) CS, its use is still inevitable in a subset of children with severe forms of RD.

Several authors have already reported the effect of human growth hormone on growth and BMD in children with rheumatic disease, treated with CS [7] [8] [9] [10] [11] [12] [13] [14]. The reported studies included variable numbers of children and treatment periods. Most of the studies are uncontrolled trials and either address growth retardation, or BMD and body composition. The aim of this project was to study the effect of human growth hormone (hGH) on growth, BMD, and body composition in children with RD taking into account the disease activity and dosage of CS in a prospective randomised controlled trial.

Material and Methods

Patients

Between March 1998 and December 1999 prepubertal patients with RD and a decrease in height of more than 0.5 SDS since the diagnosis and/or a BMD-SDS of < –1.5 SDS and on treatment with CS irrespective of the dosage were enrolled in a randomised controlled trial. Diagnostic criteria to be met were: for Juvenile Idiopathic Arthritis (JIA): DURBAN criteria [15]; for Systemic Lupus Erythematosus (SLE): the revised ACR criteria [16]; for Mixed Connective Tissue Disease (MCTD): according Sharp [17]; for dermatomyositis; according Bohan [18] [19]. Exclusion criteria were: associated diseases that might affect growth, interfere with therapy or include CNS involvement. Written informed consent from the parents and approval by the local ethical committees were obtained.

Treatment regime

Patients were randomised to an hGH-group receiving treatment with hGH 4 IU/m2/day (~ 0.045 mg/kg/day) during two years and a control-group, receiving no GH treatment. The patients were stratified for age and height standard deviation score (HSDS). The study was performed in Erasmus MC - Sophia Children's Hospital, the treatment of the RD was monitored by the patients’ own paediatric rheumatologist in different hospitals. There were no restrictions in the prescribed medication and changes in treatment were justified. Participation in other studies was not allowed.
**Anthropometrical parameters**

Height was measured at 3-month intervals. Auxological data and data on CS- and MTX-use previous to the study were collected retrospectively and expressed as SD scores and cumulative doses. Height, target height and body mass index (BMI) were expressed as SDS, using the Dutch reference growth data [20] [21]. Puberty was assessed using the stages of Tanner and Whitehouse [22]. Bone age (BA) was calculated every six months using a segmented Greulich and Pyle (GP) score [23].

**Parameters of bone mineral density and body composition**

The BMD (g/cm²) of lumbar spine and total body and body composition were measured every six months by Dual Energy X-ray Absorptiometry (DEXA) (Lunar, DPXL/PED). Results were compared with age- and sex-matched reference values [24]. BMD of lumbar spine was corrected for bone size (BMAD) [25]. Additionally all BMD and body composition parameters were corrected for bone age.

**Parameters disease activity**

Disease activity was measured six monthly with the separate variables of the PRINTO (Pediatric Rheumatology Trial Organisation) core set [26], including the following six endpoints: 1. physician global assessment of disease activity (measured on a 100 mm visual analogue scale (VAS)) 2. parent/patient assessment of the overall well-being (VAS), 3. functional ability (measured by Child Health Assessment Questionnaire (CHAQ) , ascending range 0-3 [27] ), 4. number of joints with active arthritis (range:0-75), 5. number of joints with limited range of motion (range: 0-57), 6. erythrocyte sedimentation rate (ESR) (mm/h).

The evaluation was done by an experienced paediatric physiotherapist except for the physician global assessment, which was carried out by the patient’s, own paediatric rheumatologist. In spite of the fact that some patients with SLE and MCTD have no joint involvement, we decided to use the variables of the PRINTO score for all our patients for comparability.

**Laboratory parameters**

Before the start of the study, a GH stimulation test with arginine was performed. Serum parameters of growth and bone metabolism measured six monthly were [28]: PTH; 1.25 dihydroxyvitamin D; 25-hydroxyvitamin D; carboxy terminal telopeptide of type I collagen (ICTP); procollagen type I C-terminal propeptide (PICP); calcium; alkaline phosphatas; inorganic phosphate; creatinine and IGF-I and IGFBP3. These parameters were expressed as sex- and age matched SDS using our own reference values [29]. Additionally FT4 and TSH were measured.

**Safety parameters**

Oral glucose tolerance tests (OGTT) were performed at the start and at the end of the study. The following definition of impaired glucose tolerance was used: the 120-min level higher than 7.8 mmol/liter (140mg/dl) and lower than 11.1 mmol/liter (200 mg/dl) [30].

**Statistical analysis**

Random-coefficient models (SAS PROC MIXED) were used to evaluate the effect of hGH on change in HSDS, bone mineral density and body composition. For HSDS additionally peacewise linear regression was done using pre-trial data [31]. Repeated measurement ANOVA was used to evaluate the effect on the laboratory parameters.
The Mann-Whitney U test was used to evaluate the difference between groups in mean daily doses (mg/day) of CS and MTX and the parameters of the PRINTO core set during the study. Spearman’s correlation coefficients were used to test the relationship between the change from baseline of HSDS after 2 years and several parameters (prednisone dosage, VAS, GH-peak levels after stimulation, ESR and the changes from baseline of IGF-I SDS, BMD SDS for lumbar spine and ALP SDS after 2 years). Similar coefficients were used to test the relationship between the change from baseline of BMD SDS for the lumbar spine and the change from baseline of ALP SDS after 2 years. P-values (two-sided) less than or equal to 0.05 were considered statistically significant. Power calculations had led to 20 patients. However due to a lower accrual than expected, we decided to stop the inclusion after 17 patients. This decision was taken before all data were gathered and analysed. With this reduced number differences regarding the change from baseline of HSDS between groups, expressed as effect size (i.e. difference of means divided by the standard deviation), can be detected with power 80 percent if the effect size equals 1.4.

Results

Patients

The ratio hGH-treated versus controls after randomisation was 10:7. There were nine children with systemic JIA (hGH-group: controls =7:2), two patients with polyarticular JIA ((1:1), two with MCTD (1:1), two with SLE (1:1) and two patients with Dermatomyositis (0:2). Sixteen patients completed the study. Although one patient (control group) discontinued the study after six months because of bone marrow transplantation, the data acquired were included in the analyses. During the study five children reached puberty (three from the hGH-group). The clinical characteristics of the patients at start of the study are shown in table 1. The two groups were comparable at baseline.

Three children had a decreased GH peak (< 20 IU/l) after stimulation, with normal IGF-I and IGFBP3 serum levels (hGH-group: controls = 1:2).

Table 1. Clinical characteristics of the patients at start (median + range).

<table>
<thead>
<tr>
<th></th>
<th>GH-treated group</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m: f)</td>
<td>2:8</td>
<td>2:5</td>
</tr>
<tr>
<td>Age at start (year)</td>
<td>8.0 (5.7 – 13.0)</td>
<td>8.1 (6.8 – 10.8)</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-1.4 (-3.0 – 0.1)</td>
<td>-1.9 (-2.9 – -1.0)</td>
</tr>
<tr>
<td>BMD total body SDS</td>
<td>-0.8 (-1.8 – 0.8)</td>
<td>-1.9 (-2.5 – -0.3)</td>
</tr>
<tr>
<td>BMD lumbar spine SDS</td>
<td>-1.6 (-2.3 – 0.6)</td>
<td>-1.9 (-2.7 – -0.5)</td>
</tr>
<tr>
<td>Lean body mass SDS</td>
<td>-1.9 (-2.9 – -0.0)</td>
<td>-1.9 (-3.0 – -0.9)</td>
</tr>
<tr>
<td>% Fat SDS</td>
<td>1.5 (-0.6 – 3.2)</td>
<td>0.0 (-1.5 – -3.9)</td>
</tr>
<tr>
<td>Target height SDS</td>
<td>0.4 (-1.5 – 3.1)</td>
<td>0.3 (-1.8 – 3.3)</td>
</tr>
<tr>
<td>Cumulative dosis of prednisone (mg)</td>
<td>5963 (2094 – 27864)</td>
<td>7603 (2317 – 26810)</td>
</tr>
<tr>
<td>Cumulative dosis of Methotrexate (MTX) (mg)</td>
<td>814 (180 – 2999)</td>
<td>765 (0 – 2184)</td>
</tr>
<tr>
<td>physician global assessment of disease activity (mm)*</td>
<td>66 (10 – 95)</td>
<td>19.0 (5 – 93)</td>
</tr>
<tr>
<td>parent/patient assessment of the overall well-being (mm)*</td>
<td>26 (0 – 49)</td>
<td>19.0 (0 – 45)</td>
</tr>
<tr>
<td>functional ability** (range: 0-3)</td>
<td>0.9 (0 – 2.8)</td>
<td>1.8 (0.1 – 3.0)</td>
</tr>
<tr>
<td>number of joints with active arthritis (range:0-75)</td>
<td>9 (1 – 30)</td>
<td>2 (0 –18)</td>
</tr>
<tr>
<td>number of joints with limited range of motion (range: 0-57)</td>
<td>6 (2 – 21)</td>
<td>3 (0 – 23)</td>
</tr>
<tr>
<td>erythrocyte sedimentation rate (ESR) (mm/h)</td>
<td>26.5 (3 – 77)</td>
<td>11.0 (6 – 30)</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>0.3 (-1.4 - 0.8)</td>
<td>0.1 (-0.9 – 1.2)</td>
</tr>
</tbody>
</table>

* measured on a 100 mm visual analogue scale (VAS)
** Child Health Assessment Questionnaire (CHAQ)

** Growth and bone age

A significant mean increase of HSDS was seen in the hGH-group of 0.42 SDS ± 0.16 SDS (p = 0.03) and a non-significant decrease in the controls of -0.18 SDS ± 0.11 SDS, resulting in a difference of 0.6 ± 0.19 SDS between the groups (p= 0.02).

When pre-trial growth data were included in the analysis, there was a significant change in growth at the start of the trial within the hGH-group and no significant change within the control group (figure 1a and 1b).

With correction for bone age the difference in increase in HSDS between the groups becomes even more significant (p= 0.004). The ratio change in bone age to change in chronological age was not significantly different from one in both groups.

** Bone mineral density and body composition

The hGH-group showed a significant mean increase of the BMD SDS for the lumbar spine of 0.52 ± 0.22 SDS during two years. This significance was no longer perceptible after correction for bone size. BMD for total body did not increase significantly. Controls showed no significant changes of BMD parameters. Finally changes of BMD between the groups were not significantly different (Table 2).

Table 2. Mean annual change (± SEM) in bone mineral density and body composition during 2 years of study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GH-treated group</th>
<th>Controls</th>
<th>GH-treated vs Controls (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD SDS Total body</td>
<td>-0.09 ± 0.07</td>
<td>-0.14 ± 0.14</td>
<td>0.58</td>
</tr>
<tr>
<td>BMD SDS for lumbar spine</td>
<td>0.26 ± 0.11 *</td>
<td>0.12 ± 0.13</td>
<td>0.31</td>
</tr>
<tr>
<td>BMAD SDS for lumbar spine</td>
<td>0.07 ± 0.13</td>
<td>-0.22 ± 0.20</td>
<td>0.22</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>0.32 ± 0.10 **</td>
<td>-0.10 ± 0.09</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Fat</td>
<td>-0.26 ± 0.13</td>
<td>-0.14 ± 0.36</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-0.08 ± 0.17</td>
<td>0.12 ± 0.21</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Within group significance: * p < 0.05  ** p < 0.01

Lean body mass increased significantly in the hGH-group compared to controls (0.64 ± 0.19 SDS versus -0.20 ± 0.17 in two years (p<0.01)) (Table 2). Nor the decrease in percentage fat nor the change in BMI SDS was significantly different between groups. Results were similar after correction for bone age.

** Medication, disease activity and laboratory parameters

There was no significant difference in MTX, prednisone dose or the different variables of disease activity between the groups (Table 3).
**Table 3.** Values of the different variables of the PRINTO core-set and the medication-use per day during 2 years of study (median with range of individual mean values during the study).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GH-treated group</th>
<th>Controls</th>
<th>GH-treated vs Controls (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>physician global assessment of disease activity (VAS)</td>
<td>41 (18.8 – 61.6)</td>
<td>18 (10.2 – 66.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>parent/patient assessment of the overall well-being (VAS)</td>
<td>10.2 (0.8 – 36)</td>
<td>15.7 (1 – 37.6)</td>
<td>0.75</td>
</tr>
<tr>
<td>functional ability</td>
<td>1.4 (0.1 – 2.3)</td>
<td>1.7 (0.3 – 2.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>number of joints with active arthritis</td>
<td>4.4 (0.4 – 20.0)</td>
<td>2.6 (0 – 22.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>number of joints with limited range of motion</td>
<td>7.2 (2.8 – 16.4)</td>
<td>6.6 (2.2 – 23.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>erythrocyte sedimentation rate (ESR)</td>
<td>24.1 (8.5 – 70.9)</td>
<td>12.4 (11.3 – 23)</td>
<td>0.08</td>
</tr>
<tr>
<td>Prednisone (mg/day)</td>
<td>6.1 (0 – 29.2)</td>
<td>8.0 (0.1 – 24)</td>
<td>0.52</td>
</tr>
<tr>
<td>MTX (mg/day)</td>
<td>2.4 (0.7 – 2.9)</td>
<td>2.3 (0 – 5.3)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

The mean difference in alkaline phosphatase-, IGF-I- and IGFBP3 SDS were significant between the groups. The other biochemical markers of growth and bone metabolism were not significantly different (see table 4.).

**Table 4.** Laboratory evaluation during the 2 years of study:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Difference of means (GH-treated minus Controls)*</th>
<th>GH-treated vs Controls (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICTP SDS</td>
<td>1.2 ± 0.6</td>
<td>0.06</td>
</tr>
<tr>
<td>PICP SDS</td>
<td>0.9 ± 0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Alkaline phosphatase SDS</td>
<td>1.0 ± 0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Phosphate SDS</td>
<td>0.6 ± 0.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Ca SDS</td>
<td>0.2 ± 0.4</td>
<td>0.59</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D₃ SDS</td>
<td>0.5 ± 0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>25-hydroxyvitamin D₃ SDS</td>
<td>-0.4 ± 0.3</td>
<td>0.16</td>
</tr>
<tr>
<td>IGFBP3 SDS</td>
<td>0.8 ± 0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>1.1 ± 0.3</td>
<td>0.003</td>
</tr>
<tr>
<td>FT4 SDS</td>
<td>-0.04 ± 0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>TSH SDS</td>
<td>0.1 ± 0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*All differences are adjusted for the baseline value

**Correlations**

There was a significant negative correlation ($r = -0.61; p = 0.012$) between the dosage of prednisone and the change from baseline of HSDS after 2 years in the combined groups (hGH-treated and controls). This relationship did not differ significantly between the groups. No other significant correlations were found.
Safety parameters

Treatment was well tolerated and no drug related adverse events were seen during the study period. Nine children (five in the hGH-group) showed impaired glucose tolerance at start of the study. Only three had impaired glucose tolerance after two years and no new cases were observed. None of the children developed diabetes mellitus.

Discussion

Our study is the first trial with a control group where the effect of growth hormone on growth as well as on BMD and body composition is studied. A significant positive effect of growth hormone on height SDS was seen, irrespective of disease activity, dosage of steroids and of MTX, without undue acceleration of bone maturation.

Although there was a significant increase in BMD for the lumbar spine in the hGH-group, there was no significant effect of growth hormone detectable on BMD compared with controls. On the other hand we found a significant effect on body composition, especially on lean body mass. Since the most important factor in the activation of the skeletal system is the strain of bones due to muscle contraction [32], an increase of lean body mass might positively influence the bone mineral density in the long run.

To correct for other factors influencing growth retardation and osteopenia we studied the disease itself and other medications like CS and MTX. In our study there was a significant negative correlation between prednisone and the change from baseline of HSDS after 2 years. Since there was no significant correlation between ESR and change from baseline of HSDS after 2 years in the whole group or a significant difference between the groups, the significant increase in height SDS was most likely to be an effect of growth hormone. This was also illustrated by the non-significant difference in disease activity and the use of prednisone or MTX between the groups.

The significant improvement in height found in this study concurs with other publications [7] [8] [9] [10] [11] [12] [13] [14]. Most of them are case series, varying from 7 to 20 patients with an increase of growth velocity varying between 1.9 cm and 6.7 cm per year during growth hormone treatment. These discordant results can partly be explained by the inclusion of pubertal patients and the different hGH dosages varying from 0.57 to 2 mg/m2/day. Also differences in the severity of the disease may play a role. Bechtold et al. conducted one of the two other known controlled trials to study the effect of growth hormone on growth retardation [8]. They found a relative height gain of 1.7 SDS over four years. This is slightly more than the difference in increase in HSDS of 0.6 ± 0.19 SDS over two years we found in our study and also more than the 0.13 SDS over six months Saha et al found in their placebo-controlled crossover study [13]. These differences in height gain might be due to the different duration of the study, difference in severity of the disease, different dosage of prednisone or the difference in baseline HSDS. In the study of Bechtold for example the children were shorter at start than in our study (-3.3 versus –1.9 in the control-group and –2.3 versus –1.4 in the hGH-group). This last hypothesis could however not be supported by our study in which no correlation between the baseline HSDS and the change from baseline of HSDS after 2 years was found.

The effect of hGH on bone mineral density, bone turnover and body composition has
already been described in the literature, but it was hardly ever studied in a controlled trial. Although Rooney et al. found an increase in bone mineral content (expressed per cm of vertebral height BMD, in g/cm) [10], they did not evaluate the BMD (g/cm²) itself or BMAD which are area densities derived from the bone mineral content that correct even better for bone size. In contrast to a previous study [12], the group of Czernichow et al. found in their second, more long term study an increase in bone mineral density during treatment [14]. It is however questionable whether the increase in this study might have been age related, since the SD scores for bone mineral density were expressed for weight and not for age. Also there was no control group available to be able to attribute this increase to the effect of growth hormone. The fact that there is no significant effect of hGH on bone mineral density in our study, whilst a significant effect on lean body mass was present, may indicate that a longer duration of treatment is necessary to evaluate the effect on bone mineral density. This is also supported by Bechtold et al, who found despite an increase in bone turnover, only a stabilization of bone mineral density [33].

It is assumed that disturbances in the GH-IGF-I axis are one of many factors contributing to growth retardation in children with rheumatic disease [12] [34] [35] [36] [37]. However in our study no obvious disturbances in this axis were noted. This implies that the significant effect of growth hormone on growth is not explained by this phenomenon.

This study is mainly limited by the heterogeneity in the study-population and the small number of patients. We managed however to show the effect of growth hormone on growth, bone density and body composition by using age- and sex-matched references and the same core set variables for disease activity for the different diseases.

In conclusion, hGH has a significant effect on growth, irrespective of the disease activity and the dosage of steroids and MTX used. There is also a significant effect on the body composition (especially on the lean body mass), but a longer duration of treatment might be necessary to evaluate the effect of hGH on bone mineral density.

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Competing interests
None declared

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What is already known on this subject

In children with severe rheumatic disease a beneficial effect of human growth hormone (hGH) on corticoid induced growth retardation has been reported, mostly in trials without a control group.

The effect of hGH on bone mineral density, bone turnover and body composition has previously been described, but remains questionable.

What this study adds

This randomised controlled trial shows a significant effect of hGH on growth, irrespective of the disease activity and the dosage of steroids and MTX used.

There is a significant effect on the body composition (especially on the lean body mass), but a longer duration of treatment might be necessary to evaluate the effect of hGH on bone mineral density.

Figure legends

Figure 1

Individual levels of height SDS per group before and during the study period
GH-treated group
b. Controls
Time=0 denotes the start of the study. The solid line represents the regression line of HSDS within the group with a breakpoint at time=0.
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