ORIGINAL ARTICLE

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

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Background: 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.

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

Results: During the two year study period the disease activity, and 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) and a non-significant decrease in the controls (-0.18 ± 0.11 SDS). 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 controls (0.64 ± 0.19 SDS versus -0.20 ± 0.17 SDS), while the decrease in percentage fat was not significant.

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

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 non-steroidal anti-inflammatory drugs in combination with corticosteroids (CS), sulfasalazine, methotrexate (MTX), and recently TNF α blocking agents ("biologicals", such as 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 CS are a decline of growth velocity and osteoporosis.² Diminished physical activity associated with arthritis negatively influences weight bearing and movement, both of which play a role in bone turnover.³ Moreover, chronic inflammation inhibits the GH-IGF-I axis resulting in a decrease in bone mineral density (BMD) and growth retardation.^{4–6} In spite of the development of new treatments and efforts to avoid long term therapy with high doses of CS, their 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.^{7–14} The reported studies included variable numbers of children and treatment periods. Most of the studies were uncontrolled trials and addressed either 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.

METHODS

Patients

Between March 1998 and December 1999, prepubertal patients with RD and a decrease in height of more than 0.5

SDS since diagnosis and/or a BMD-SDS of the lumbar spine of <-1.5 SDS, and who were being treated with CS, were enrolled in a randomised controlled trial. Diagnostic criteria to be met were: the DURBAN criteria¹⁵ for juvenile idiopathic arthritis (JIA); the revised ACR criteria¹⁶ for systemic lupus erythematosus (SLE); the criteria of Sharp and colleagues¹⁷ for mixed connective tissue disease (MCTD); and the criteria of Bohan and Peter^{18, 19} for dermatomyositis. 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 or 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; treatment of the RD was monitored by the patients' own paediatric rheumatologists 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 three month intervals. Auxological data and data on CS and MTX use previous to the study were

Abbreviations: BMD, bone mineral density; CS, corticosteroid; ESR, erythrocyte sedimentation rate; hGH, human growth hormone; HSDS, height standard deviation score; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; MTX, methotrexate; RD, rheumatic disease; SDS, standard deviation score; SLE, systemic lupus erythematosus; VAS, visual analogue scale

Table 1 Clinical characteristics of the patients at the start of the study

	GH treated group	Controls
Sex (M:F)	2:8	2:5
Age at start (year)	8.0 (5.7 to 13.0)	8.1 (6.8 to 10.8)
Height SDS	-1.4 (-3.0 to 0.1)	-1.9 (-2.9 to -1.0)
BMD total body SDS	-0.8 (-1.8 to 0.8)	-1.9 (-2.5 to -0.3)
BMD lumbar spine SDS	-1.6 (-2.3 to 0.6)	-1.9 (-2.7 to -0.5)
Lean body mass SDS	-1.9 (-2.9 to -0.0)	-1.9 (-3.0 to -0.9)
% fat SDS	1.5 (-0.6 to 3.2)	0.0 (-1.5 to -3.9)
Target height SDS	0.4 (-1.5 to 3.1)	0.3 (-1.8 to 3.3)
Cumulative dose of prednisone (mg)	5963 (2094–27864)	7603 (2317–26810)
Cumulative dose of methotrexate (MTX) (mg)	814 (180–2999)	765 (0–2184)
Physician global assessment of disease activity (mm)*	66 (10–95)	19.0 (5–93)
Parent/patient assessment of the overall wellbeing (mm)*	26 (0–49)	19.0 (0–45)
Functional ability† (range: 0–3)	0.9 (0–2.8)	1.8 (0.1–3.0)
Number of joints with active arthritis (range: 0–75)	9 (1–30)	2 (0–18)
Number of joints with limited range of motion (range: 0–57)	6 (2–21)	3 (0–23)
ESR (mm/h)	26.5 (3–77)	11.0 (6–30)
IGF-I SDS	0.3 (-1.4 to 0.8)	0.1 (-0.9 to 1.2)

Results expressed as median (range).

*Measured on a 100 mm visual analogue scale (VAS).

†Child Health Assessment Questionnaire (CHAQ).

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/cm^2) 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 of 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 end-points: (1) physician global assessment of disease activity (measured on a 100 mm visual analogue scale (VAS)); (2) parent/patient assessment of the overall wellbeing (VAS); (3) functional ability (measured by Child Health Assessment Questionnaire (CHAQ), ascending range 0–3²⁷); (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: 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 phosphatase, inorganic phosphate, creatinine, IGF-I, and IGFBP3.²⁸ These parameters were expressed as sex and age matched SDS using our own reference values.²⁹ Additionally FT4 and TSH were measured.

Figure 1 Individual levels of height SDS per group before and during the study period. (A) 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.

Safety parameters

Oral glucose tolerance tests (OGTT) were performed at the start and end of the study. The following definition of impaired glucose tolerance was used: the 120 minute level was >7.8 mmol/l (140 mg/dl) and <11.1 mmol/l (200 mg/dl).³⁰

Table 2 Mean annual change ($\pm$ SEM) in bone mineral density and body composition during two years of study

Parameter	GH treated group	Controls	GH treated v controls (p value)
BMD SDS for total body	-0.09 ± 0.07	-0.14 ± 0.14	0.58
BMD SDS for lumbar spine	$0.26 \pm 0.11^*$	0.12 ± 0.13	0.31
BMAD SDS for lumbar spine	0.07 ± 0.13	-0.22 ± 0.20	0.22
Lean body mass	$0.32 \pm 0.10^{**}$	-0.10 ± 0.09	<0.01
% fat	-0.26 ± 0.13	-0.14 ± 0.36	0.76
BMI SDS	-0.08 ± 0.17	0.12 ± 0.21	0.46

Within group significance: * $p < 0.05$, ** $p < 0.01$.

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, piecewise linear regression was also 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 relation between the change from baseline of HSDS after two 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 two years). Similar coefficients were used to test the relation between the change from baseline of BMD SDS for the lumbar spine and the change from baseline of ALP SDS after two years. Values of p (two sided) which were ≤ 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 (that is, difference of means divided by the standard deviation), can be detected with power 80% if the effect size equals 1.4.

RESULTS

Patients

The ratio hGH treated patients to controls after randomisation was 10:7. There were nine children with systemic JIA (hGH group:controls = 7:2), two with polyarticular JIA (1:1), two with MCTD (1:1), two with SLE (1:1), and two 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 the 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).

Growth and bone age

A significant mean increase of HSDS was seen in the hGH group of 0.42 ± 0.16 SDS ($p = 0.03$) and a non-significant decrease in the controls of -0.18 ± 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 (fig 1).

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 in BMD parameters. Finally, changes in BMD between the groups were not significantly different (table 2).

Lean body mass increased significantly in the hGH group compared to controls (0.64 ± 0.19 SDS versus -0.20 ± 0.17 SDS in two years, $p < 0.01$) (table 2). Neither the decrease in percentage fat nor the change in BMI SDS was significantly different between groups. Results were similar after correction for bone age.

Table 3 Values of the different variables of the PRINTO core set and medication use per day during two years of study

Parameter	GH treated group	Controls	GH treated v controls (p value)
Physician global assessment of disease activity (VAS)	41 (18.8–61.6)	18 (10.2–66.4)	0.23
Parent/patient assessment of overall wellbeing (VAS)	10.2 (0.8–36)	15.7 (1–37.6)	0.75
Functional ability	1.4 (0.1–2.3)	1.7 (0.3–2.7)	0.19
Number of joints with active arthritis	4.4 (0.4–20.0)	2.6 (0–22.4)	0.33
Number of joints with limited range of motion	7.2 (2.8–16.4)	6.6 (2.2–23.2)	0.96
ESR	24.1 (8.5–70.9)	12.4 (11.3–23)	0.08
Prednisone (mg/day)	6.1 (0–29.2)	8.0 (0.1–24)	0.52
MTX (mg/day)	2.4 (0.7–2.9)	2.3 (0–5.3)	0.64

Results expressed as medians (range of individual mean values during the study).

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).

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).

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 two years in the combined groups (hGH treated and controls). This relation 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 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 such as CS and MTX. In our study there was a significant negative correlation between prednisone and the change from baseline of HSDS after two years. Since there was no significant correlation between ESR and change from baseline of HSDS after two 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.^{7–14} Most are case series, of 7–20 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. Differences in the severity of the disease may also 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 which 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 *et al*, for example, the children were shorter at the 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 was found between the baseline HSDS and the change from baseline of HSDS after two years.

The effect of hGH on bone mineral density, bone turnover, and body composition has already been described in the literature, but 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 Czernichow *et al* found in their second, longer 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, while 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 stabilisation of bone mineral density.³³

It is assumed that disturbances in the GH-IGF-I axis is one of many factors contributing to growth retardation in children with rheumatic disease.^{12 34–37} 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 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 body composition (especially on lean body mass), but a longer duration of treatment might be necessary to evaluate the effect of hGH on bone mineral density.

Table 4 Laboratory evaluation during the two years of study

Parameter	Difference of means (GH treated minus controls)*	GH treated v controls (p value)
ICTP SDS	1.2 ± 0.6	0.06
PICP SDS	0.9 ± 0.5	0.06
Alkaline phosphatase SDS	1.0 ± 0.4	0.03
Phosphate SDS	0.6 ± 0.4	0.19
Ca SDS	0.2 ± 0.4	0.59
1,25-dihydroxyvitamin D ₃ SDS	0.5 ± 0.2	0.05
25-hydroxyvitamin D ₃ SDS	-0.4 ± 0.3	0.16
IGFBP3 SDS	0.8 ± 0.3	0.01
IGF-I SDS	1.1 ± 0.3	0.003
FT4 SDS	-0.04 ± 0.4	0.9
TSH SDS	0.1 ± 0.7	0.9

*All differences are adjusted for the baseline value.

What is already known on this topic

- In children with severe rheumatic disease, a beneficial effect of hGH on corticosteroid 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 body composition (especially on 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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