CHILDREN BORN SMALL FOR GESTATIONAL AGE, FIVE YEARS EXPERIENCE WITH GROWTH HORMONE THERAPY

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Aim: Recombinant Human Growth Hormone (rhGH) is an effective treatment for short children born small for gestational age (SGA) who fail to demonstrate catch-up growth by 2-4 years of age. These children usually don’t have classical GH deficiency, but either low GH secretion or reduced sensitivity to GH. The goals of therapy are to achieve a normal height in early childhood and an adult height within the normal target range. We assessed the efficacy and safety profile in the first 5 years of rhGH treatment in ten SGA children.

Material and methods: The study enrolled 10 SGA children (6 boys, 4 girls). All patients were given a mean dose of 0.35mg/kg/wk. and followed for a period of minimum 5 years (mean 5.68 yrs.).

Results: The mean height expressed in standard deviations (SD) raised from -2.43 at diagnosis to +0.28 after 5 years. In the first 5 years of therapy there were no cases of diabetes mellitus or impaired glucose tolerance, 2 (20%) patients presented impaired fasting glucose, 1 (10%) patient developed hypothyroidism and 4 (40%) patients presented transitory subclinical hypothyroidism. Mean IGF-1 values were higher, but not exceeding +2DS. Conclusions: GH therapy is reasonably safe and effective in increasing linear growth in children born SGA who fail to have catch-up growth. Maximum height velocity was registered in the first year of treatment, 11.76 cm/year and declined in time. Adverse events due to GH treatment were no more common in the SGA population than in GH-deficient children.

Keywords: SMALL FOR GESTATIONAL AGE, RECOMBINANT HUMAN GROWTH HORMONE.

Many children with short stature do show compromised adult height relative to mid parental height for age, sex, and population group (1). When children with short stature have been born with a low weight and/or length, they are classified as short associated with being small for gestational age (SGA). International Societies of Pediatric Endocrinology and the Growth Hormone Research Society, as well as the International Small for Gestational Age Advisory Board, recommended that the term refer to infants whose birth weights and/or lengths are at least two standard deviation

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(SD) units less than the mean for gestational age (1,2). According to this definition, approximately 3%-10% of newborns are considered SGA. While most of these infants undergo catch-up growth, 10%-15% remain small for their age at the age of 2 years. In addition to short stature, SGA infants may be predisposed to altered body composition and (in adult life) hypertension and cardiovascular disease (1, 3). Data from epidemiological studies indicate that children born SGA are also at increased risk of insulin resistance and type 2 diabetes in adulthood (1). There is now evidence for an increased prevalence of metabolic syndrome among adults who were born SGA (4). Important is that their height, weight, and body mass index are closely monitored to prevent excessive weight gain, as children born SGA who catch up in weight and height are at a higher risk than those without catch-up (5). In summary, SGA is associated not only with shorter than average height, but also with potential health disadvantages, such as reduced body fat and a lack of appetite as compared with individuals who were not born SGA; there is also an increased prevalence of metabolic disorders in later life among patients born SGA as compared with those born AGA. Being born SGA is associated with lower cognitive ability in mathematics and reading comprehension and with more emotional, conduct, and attention deficit hyperactivity disorders. A relatively recent study (6) showed low values of psychomotor development and IQ in 60 children born with intrauterine growth restriction (IUGR) aged between 3 months and 16 years. The Wechsler Intelligence Scale for Children scores showed a slight worsening. The impact on the IQ seems to be inherent to the condition of being small at birth and not to the growth rate. In healthy people, Growth hormone (GH) and Insulin-like growth factor (IGF) interact to regulate growth. In utero, IGF-I, IGF-II and insulin are the key factors in regulating fetal growth, with GH having little effect. Postnataally, the contribution of IGF-I becomes more important than that of IGF-II, and neonates with growth restriction have lower IGF-I levels than neonates with a normal growth. Importantly, it has been reported that a high endogenous GH secretion significantly increases the IGF-I levels in short GH-sufficient neonates born SGA at 3 days postnatally as compared with AGA controls (7). This is evidence for a functionally activated GH-IGF-I axis in SGA neonates (8). Approximately 60% of the children with a persistent short stature who were born SGA have an abnormal GH secretion and reduced IGF levels (9). Although children with a short stature who were born SGA frequently have GH levels lower than normal, most are not usually classified as being GH deficient by recognized criteria. The status of the GH-IGF axis at birth or in early postnatal life is not predictive of later growth, and therefore hormone measurements in the SGA infant or child are not indicated in routine care. Early evaluation of short children born SGA is recommended, and those under 2 years of age with a current length below −2.5 SD should be referred for evaluation. Over the last 30 years, several recombinant human growth hormones (rhGH, Somatropin) products have been approved for the treatment of children with growth disorders associated with short stature, and multiple studies, both observational and randomized, have established the efficacy and safety of rhGH products. 10% of SGA babies fail to show catch-up growth despite
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good nutrition after birth. They continue to grow at a percentile that is lower than −2 SD and their target height percentile. SGA babies with birth length more than −2 SD below the mean have a 7 times higher risk of having short final height, and those with a birth weight more than −2 SD below mean have a 5 times higher risk, indicating that birth length has greater influence on final height than the weight. Of the infants who do not show catch-up growth, 50% end up as short adults. They constitute 14 - 22% of short adults (10). Recombinant human Growth Hormone has been used to help short SGA children achieve catch-up growth. In July 2001, GH was approved by the US Food and Drug Administration for the long-term treatment of growth failure in children who are born SGA and do not achieve catch-up growth by 2 years.

MATERIAL AND METHODS
Observational study on ten pre-pubertal children (Tanner stage I) born SGA with growth disturbances defined as current height standard deviation score (HSDS) \(\leq -2.5\) (and parental adjusted SDS \(\leq -1\)) for chronological age and sex (tab. I). Patients were treated with rhGH 0.035 mg/kg/day by subcutaneous injection in the evening. The objectives include an evaluation of efficacy through changes in height parameters; measurement of rhGH-induced serum markers IGF-I; incidence and adverse events (AEs).

TABLE I.
Data from the first 5 years of rhGH therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 year</th>
<th>2 yrs.</th>
<th>3 yrs.</th>
<th>4 yrs.</th>
<th>5 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age (yrs.)</td>
<td>6.29</td>
<td>7.29</td>
<td>8.29</td>
<td>9.29</td>
<td>10.29</td>
<td>11.29</td>
</tr>
<tr>
<td>Bone age (yrs.)</td>
<td>4.05</td>
<td>4.75</td>
<td>5.56</td>
<td>7.15</td>
<td>9.3</td>
<td>11.05</td>
</tr>
<tr>
<td>Mean IGF-1 values (ng/ml and SD)</td>
<td>77.5 (+0.24)</td>
<td>305.38 (+1.49)</td>
<td>258.71 (+1.54)</td>
<td>329.85 (+1.26)</td>
<td>412.44 (+1.47)</td>
<td>476.55 (+1.85)</td>
</tr>
<tr>
<td>Height (SD)</td>
<td>-2.43</td>
<td>-1.37</td>
<td>-0.91</td>
<td>-0.68</td>
<td>-0.43</td>
<td>0.28</td>
</tr>
<tr>
<td>Growth velocity (cm/yr)</td>
<td>-</td>
<td>11.76</td>
<td>9.24</td>
<td>8.16</td>
<td>7.68</td>
<td>6.24</td>
</tr>
</tbody>
</table>

Another objective was to evaluate the long-term effect of rhGH treatment on the development of diabetes mellitus in short children born SGA. Height was measured in cm and HV calculated. HSDS and HV were assessed at baseline and at 6-month intervals. To determine bone age, X-rays of the left hand and wrist were obtained at baseline and every year thereafter. IGF-I was measured at screening and at every 6 months thereafter. Fasting plasma glucose, 2-h OGGT, HbA1c were measured at baseline, and annually thereafter. All AEs were recorded at each visit and their incidence was reported. Physical examinations and vital signs were performed at each visit. Hematology, blood chemistry, thyroid function tests - free thyroxine (FT4) and thyroid stimulating hormone (TSH) levels, lipids were assessed at baseline, at every 6 months. Paired t tests were used to calculate p values, with statistical significance defined as p<0.05.

RESULTS
Body height increased steadily throughout treatment period; the mean height standard deviation score improved by 2.71, from -
2.43 at baseline to +0.28 at 5 years of therapy; the changes in HSDS decreased with time (fig. 1). Mean height velocity was maximum in the first year (11.76 cm/year), decreasing in the second (9.24 cm/year), third (8.16 cm/year), fourth (7.68 cm/year) and fifth year of treatment (6.24 cm/year). Growth velocity decreased slightly but remained higher than at baseline (p<0.0001) (fig. 2).

Chronological age at therapy initiation varied between 4 and 12 years (mean 6.29 yrs.). Bone age at diagnosis was late by a mean value of 2.24 years, decreasing after 5 years of treatment at a mean value of 0.24 years (fig. 3). IGF-I serum level indicated that at baseline most patients had low (≤2 SD) IGF-I levels. During the treatment IGF1 has normalized and even has risen above normal. Mean IGF-1 values were higher than normal range after five years, but not exceeding +2DS (fig. 4).

In the first 5 years of therapy there were no cases of diabetes mellitus or impaired glucose tolerance (glucose between 140-200 mg/dl at OGTT; normal values of HbA1c). Two (20%) patients presented impaired fasting glucose (fasting glucose
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between 100-126 mg/dl). One (10%) patient developed hypothyroidism. Four (40%) patients presented transitory subclinical hypothyroidism (elevated TSH, normal FT4 values, no clinical signs) (fig. 5).

**DISCUSSION**

Early initiation of rhGH therapy has as result the complete recovery of statural deficit in 5 years, according to growth prognosis calculated by parental heights. Growth response to GH treatment of non-GH deficient SGA children was done by Zegher et al (11). The analysis revealed that GH was an effective treatment for normalizing short stature in non-GH deficient SGA children during early childhood and puberty. According to consensus guidelines, a change in HVSDS of more than +0.5 within the first year of GH treatment is a growth response (1). In a large international cohort of children born SGA, HVSDS had to be at least +1 after the first year of treatment for patients to be eligible to continue with therapy; therefore, all patients regarded as responders in the present study achieved a growth response as defined in the consensus guidelines (3). Analysis of data from KIGS (Kabi-Pharmacia International Growth Study database) (12), which included data from 613 children born SGA who failed to manifest spontaneous catch-up growth, revealed that the age at which GH therapy was started was second only to dosage as the most important predictor for response. During the 1st year of therapy, the response to GH correlated negatively with age at initiation of treatment. The treatment response during the 2nd year was best predicted by a three-parameter model: HV during the 1st year of treatment, age at the start of treatment, and rhGH dose. The study confirmed the superior efficacy of beginning therapy earlier and with higher doses of rhGH treatment as compared with delaying therapy or using lower doses (3, 4, 13). An independent, international SGA Advisory Board (2) and the 2006 consensus meeting of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society (1) both developed a consensus for management of short children who were born SGA. Therapy was recommended for short children born SGA who do not manifest spontaneous catch-up growth by the age of 2-4 years. It was concluded that therapy with GH is effective and safe. The International SGA Advisory Board (4) recommended the initiation of rhGH therapy at 0.48 mg/kg/week; Long-term continuous treatment is effective, even at a dose of 25 µg/kg/day. Bone age for skeletal maturation should be done, although it is not a good predictor of adult height. Our study limitations, like many others, include the lack of a control group and the age of patients when rhGH treatment was initiated. However, the clear treatment benefits observed in most patients’ deficiency.

**CONCLUSIONS**

In our study GH therapy was reasonably safe and effective in increasing linear growth in children born SGA who fail to have catch-up growth. Maximum height velocity was registered in the first year of
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treatment, 11.76 cm/year and declined in time. No severe adverse events were regis-
tered. No malignancies were observed to date.

REFERENCES


