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THE USE OF GH AS A PHARMACOLOGICAL AGENT (MINIREVIEW)

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Growth hormone (GH) has been traditionally used as a drug for substitution therapy of GH deficiency, but since the wide availability of biosynthetic GH it has also been used as a pharmacological agent. In this report the presently available data are reviewed.

1. Turner syndrome and mixed gonadal dysgenesis

Mean final height of women with Turner syndrome is about 21 cm lower than that of women in the general population (RONGEN-WESTERLAKEN et al. 1997), and there is no doubt that many of these women consider their short stature a significant handicap. Multiple clinical trials have been performed (although only two of them were controlled) with various regimens of GH, some in combination with oxandrolone, but always combined with low dose estrogen substitution starting in late adolescence (from 12-15 years onwards). The general conclusion is that if GH (in a dosage of approx 28 IU/m^2/week or 1 IU/kg/week) is not started too late (preferably before 8 years of age), and if low-dose estrogen (0.05 µg/kg/d or an equivalent dose of natural estrogens) is not started too early (preferably not before 14 years of age), final height is increased by an average of 8 cm. The addition of oxandrolone could further increase this to an average of 10 cm (ROSENFELD et al. 1998). When GH is started later and/or estrogen is given earlier and/or at a higher dose, the final height gain is between 3-8 cm (BROECK et al. 1995). To date, controlled studies on the effect of GH treatment on quality of life during and after therapy have not been reported. With respect to short-term side effects, the elevated serum insulin levels should be mentioned, the consequences of which are not yet clear. In most industrialized countries the estimated benefit of GH therapy has been considered sufficient to counterbalance the very high costs involved, although it cannot be ruled out that in the future long-term consequences could be detected which would change the balance. There is no consensus about the cost-benefit ratio of oxandrolone addition. The benefits include approximately 2 cm additional height gain and a shorter period of treatment (thus less expenses for GH), at a cost of possible side-effects of this (in many countries) unregistered drug. While there is no doubt that the originally used dosage of oxandrolone (0.125 mg/kg/d) frequently caused disturbing side effects, opinions differ about the safety of the presently used dosage (0.05-0.1 mg/kg/d). Another unsettled issue is whether the benefit of starting late with low-dose estrogens (which appears to increase height gain with a few cm) is greater than the potential deficit of bone mass accretion (with an increased tendency to osteoporosis as a long-term consequence). With or without GH treatment, girls with Turner have a higher frequency of autoimmune hypothyroidism and celiac disease, which should therefore be regularly checked (NIENHUIS et al 1993).

Girls in whom the karyotype shows Y-chromosome remnants have often been excluded from clinical trials, because they were thought to have an increased risk of malignancies. The cases who have been treated have shown a similar growth response. There is so far no indication that GH would increase the risk of malignancies. A similar situation exists in individuals with mixed gonadal dysgenesis (X/XY mozaicism with variable masculinisation). Also in these children the growth response to GH is similar to that

seen in classical Turner syndrome. If a (remnant of) a Y-chromosome is present, gonadectomy is usually advocated.

2. Chronic renal failure

Many children with chronic renal failure (CRF) show a severe growth retardation, in spite of all improvements to the medical treatment over the last decennia. In 75 % of the patients who had received their first cadaveric renal transplant before the age of 15 years, final height remained below the 3rd percentile. Several controlled studies have now irrefutably shown that GH in a dosage of 28 IU/m^2/wk increases height velocity significantly (Hokken-Koelega et al. 1991), and in the meantime sufficient data have been collected to state that bone maturation is not advanced inappropriately, and that final height is definitely improved by GH therapy. No deleterious effect on renal function has been detected.
The reason why GH is so efficacious in this condition is not completely clear, but at present the most likely explanation is that GH treatment increases the serum free IGF-I levels, which are low in the untreated state by very high levels of serum IGFBP-3 and -1. The present guideline is to start GH treatment in children with CRF if growth is deviating from its percentile over a period of more than 6 months, and to continue until renal transplantation. In most industrialized countries GH is registered for this indication. Even after a successful renal transplantation, the majority of the children and adolescents do not show a significant catch-up growth, except if treated with GH (Hokken-Koelega et al. 1994). In children as well as adolescents in an advanced stage of puberty and with advanced bone age, spectacular growth responses to GH therapy have been observed, without detectable negative effects on allograft function or rejection risk. Also in these conditions, a dose of 28 IU/m^2/week appears optimal.

3. Intrauterine growth retardation

Children born with a small length and/or weight for gestational age form a heterogeneous group. In some of these infants growth retardation appears the result of maternal factors, such as poor placental function, toxins or diseases. In this subgroup the growth disturbance can be considered as acquired (albeit very early), thus strictly speaking a "secondary" growth disorder. In other infants the growth retardation appears part of an intrinsic abnormality of the fetus, such as chromosomal disorders or dysmorphic syndromes. For example, children with Silver-Russell syndrome, a clinical entity with dysmorphic features and IUGR, are generally included in clinical trials on IUGR. In many cases the specific cause (extrinsic or intrinsic) remains unknown.

The natural history in terms of growth of infants born with IUGR is that 85 % catches up into the population reference range. In the remaining 15 % height remains below the 3rd percentile, but usually keeps running parallel to it (Hokken-Koelega et al. 1995). The onset of puberty is usually in the early normal range, and the pubertal height gain is relatively low. Final height in almost all cases is below the 3rd percentile. Studies into the GH secretion pattern have generally shown an irregular and often low secretion, in contrast with the absence of the classical clinical signs of GHD.

Many clinical trials with GH treatment in various designs and dosage modalities have been performed, and without exception the average height velocity increased substantially, in a dose dependent manner (De Zegher et al. 1997). Also without exception, bone age advanced more than 1 "year" per year, but so far the predicted adult height has tended to increase. Final height data are not available yet, and it may well be that temporary addition of GnRH analogues would be beneficial in this patient group to extend the period that growth can take place. Relevant short term side effects have not been noted, but theoretically there is reason for concern that GH treatment in these children who already have a tendency towards insulin insensitivity might increase their risk to develop "syndrome X" later on. Due to the unavailability of final height results and the uncertainties about the metabolic effects, persistent short stature after IUGR is so far not accepted as an indication for GH therapy.

4. Idiopathic short stature

Average height velocity in the first year of GH treatment usually almost doubles, with an apparent log dose-response relationship. In the second year of treatment height velocity drops to 5.1-6.7 cm/year and in the consecutive years height velocity is only

slightly faster than normal. Bone age advances more than chronological age (approx 1.25 "year" per year). The average net effect is 3-5 cm in terms of final height gain, with an apparent dose-response effect (Wit et al. 1996). This effect is considered by many clinicians as insufficient to counterbalance the vast costs. However, one should note that only in extreme cases of GHD a good estimate has been made of the benefit of GH therapy (approx. 30 cm). In less severe cases of GHD the height gain will certainly be less, and it is likely that the hazy separation between GHD and non-GHD finds a parallel in a continuous spectrum of final height gain. The main challenge is thus to find a better selection procedure for those children from the heterogeneous group of ISS patients in whom an insufficient GH secretion plays a central role and GH-responsiveness is good, and who therefore may respond better than average, and possibly not worse than some cases with partial GHD.

For the children with familial and non-familial ISS without pubertal delay, and particularly in those with a relatively early puberty, another therapeutical option has been tried, that is a combination of GH in a relatively high dose (28 IU/m^2/wk) which GnRH analogues for 2-3 years (Saggese et al. 1995). Children with ISS who are short at the onset of a relatively early puberty can be rather certain to be short as an adult, if untreated. Theoretically this treatment regimen should be able to result in a better adult height, but the results of controlled trials on final height are still awaited.

5. Dysmorphic syndromes

5.1. Down syndrome

Most numerical chromosomal disorders are characterized by short stature, and multiple other clinical signs. Besides in Turner syndrome, GH treatment has been studied in children with Down syndrome. Untreated, growth is particularly slow in the first 3 years of life and in puberty. Average final height is approx 3 SD below the population's mean (Cremers et al. 1996). The incidence of auto-immune hypothyroidism, celiac disease and leukemia is increased. GH secretion appears normal, and a low serum IGF-I has been described. The role of short stature in the personal experience of children with Down syndrome is difficult to assess.

Clinical trials with GH have shown that height velocity doubles in the first year of therapy and then gradually wanes off (Anneren et al. 1993). No improvement of the intellectual or social development has been observed. The potential benefit is considered small, as even if final height would increase by 5 cm it seems dubious whether the young adult with Down syndrome would experience this as an improvement of quality of life. At the cost side, on top of the burden for the patient (thousands of injections) and the society (financial) one should take into account that in Down syndrome the risk of leukemia is increased, and theoretically may further increase by GH treatment.

5.2. Noonan syndrome

Noonan syndrome is characterized by dysmorphic features, congenital disorders of the right heart axis, and short stature (approx 17 cm below the population's mean). GH provocation tests usually reveal normal results, but in some cases endogenous GH secretion and serum IGF-I are low. The response to GH treatment has been quite similar to that in Turner syndrome, but final height results are still awaited (Romano et al. 1996).

5.3. Prader-Willi-Labhart syndrome

This syndrome is characterized by an infantile hypotonia, cerebral dysfunction and behaviour problems, dysmorphic features, obesity, hypogonadism and poor growth. In many cases a 15q deletion or paternal disomy is found. Mean final height is approximately 20-25 cm less than the population's mean. In many cases low GH levels after stimulation tests and during 24-hr profiles have been found, not only in obese children. The short-term response to GH therapy appears good, but no results on final height have been reported (Carrel et al. 1999). In the cost-benefit ratio similar arguments play a role as discussed in the paragraph on Down syndrome.

6. Skeletal dysplasia

In disproportionate children one should actively search for signs of one of the many skeletal dysplasias. In general, total body stature is short, with a variety of disorders in the size of the skull, trunk

and limbs, resulting in abnormal proportions. An extensive radiological screening in combination with a detailed set of anthropometry and DNA studies can often lead to a diagnosis.

Achondroplasia is characterized by an enlarged skull and short limbs, resulting in a total body stature of 40-45 cm less than the population's mean. There are a number of neurosurgical and orthopedic complications. The condition is caused by a mutation in the FGF receptor 3. During the first years of GH therapy height velocity is significantly increased, but no results of final height are known (Hagenaes et al. 1996; Stamoyannou et al. 1997). Body proportions did not improve. Leg-lengthening operations have shown their efficacy, but the severity of the procedure and the possible complications have limited its use.

Hypochondroplasia is a much more variable condition, in which body proportions can be still within the normal range before puberty (Appan et al. 1990). In about 50% of the cases mutations in the FGF receptor 3 have been found. Most of the reported short term results of GH therapy are little encouraging for a significant effect on final height (Appan et al. 1990; Hagenaes et al. 1996), but recently better results have been reported by a Japanese group (Seino et al. 1999).

In **pseudohypoparathyroidism type 1**, final height is severely compromised (about 22 cm lower than the population). In a case report little effect of GH was found.

Osteogenesis imperfecta is characterized by multiple fractures and short stature. GH was tried in some cases. Height velocity increased, but also the number of fractures (Kinugasa et al. 1991; Antoniazzi et al. 1996).

7. Disorders in bone metabolism

Out of the various disorders in this diagnostic class (e.g. mucopolysaccharidoses, mucolipidoses) only in hypophosphatemic rickets GH treatment has been tried. In this X-linked disorder there is a defect in the tubular phosphate reabsorption in the kidney, leading to hypophosphatemia and rickets, normal serum calcium, insufficient bone mineralisation and short stature. The conventional therapy consists of high doses of phosphate orally at frequent intervals, in combination with high dose calcitriol. Final height is usually below the 3rd percentile. GH appears to have a positive additive effect on serum phosphate levels and growth, but no data is available about final height.

8. Iatrogenic causes

8.1. Drugs

Steroids can, already in dosages which are not far above the substitution level, inhibit growth. This effect can be seen most clearly in children treated with high doses of steroids as part of treatment protocols for malignancies, juvenile chronic arthritis, collagen disorders, severe asthma and for post-transplant regimens. However, even with locally administered steroids, such as inhalation steroids for moderate forms of asthma, growth retardation can be seen, with a remarkable interindividual variation. For children who underwent renal transplantation the efficacy of GH in improving growth and final height has been clearly documented (Hokken-Koelega et al 1994). In other patient groups, there are also suggestions that GH can for some part neutralize the growth-inhibiting effects of steroids (Touati et al. 1998). The independent negative effect of cytostatics on growth is less well documented, but appears to exist as well. No data on the effect of GH in such cases is available.

8.2. Irradiation

Skull irradiation with a dose >30 cGy, which is often part of the treatment protocol of brain tumors, virtually certainly leads to multiple pituitary deficiency with time. However, also lower doses of 18-24 cGy have been shown to reduce the endogenous GH secretion, and sometimes lead to other hormonal deficiencies. Total body irradiation can also lead to neurosecretory dysfunction, but also to direct damage to the growth plates in extremities and trunk. Final height is reduced in these children, particularly because of a reduced pubertal height gain. GH treatment protocols are being carried out, but no final height data are available yet (Sulmont et al. 1990).

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