Review Article

GROWTH HORMONE THERAPY: CURRENT STATUS

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Growth hormone (GH) derived from human cadavers was initially used in clinical trials in children with classical growth hormone deficiency (GHD)(1). Since the supply was far below the demand, its use was restricted to children with documented GHD under the supervision of national agencies(2,3). The diagnosis of GHD in these children was usually made when there was failure of secretion of adequate quantities of GH in response to at least two definitive stimuli(4). The clinical supportive criteria included a growth velocity subnormal for age and epiphyseal maturation. The initial dose recommended was 0.06-0.1 IU/kg per dose, given three times weekly. The pretreatment growth rate of 3-4 cm/year was expected to accelerate to 8-10 cm/year during the first year of this treatment. The dose was increased subsequently due to the decline of the effect on prolonged therapy.

Doubts were raised about treatment in 1985 when Creutzfeldt-Jakob disease (CJD), a slow virus disease affecting the central nervous system, was detected in 4 patients in UK and USA on human cadaveric GH therapy(5). As a result, this product was banned from the world market following confirmatory investigations.

By the early 1980s, recombinant DNA technology had revolutionized the understanding and ability to control the production of proteins. Efforts were made to produce bio-synthetic growth hormone using a specific strain of *Escherichia coli* as a host and a vector plasmid containing the appropriate information. The first biosynthetic GH thus produced was identical to pituitary growth hormone except for an additional methionine residue at the N-terminal. Extensive experimental trials did not show any toxic or mutagenic effects(6). Fermentation and purification by ion exchange, gel filtration and precipitation helped in removal of impurities such as *E. coli* proteins resulting in a highly purified form of methionyl GH (Met-GH, Somatonorm). The first human trial started in 1981. Clinical studies worldwide demonstrated that this preparation when administered subcutaneously or intramuscularly to patients with growth hormone deficiency produced a height velocity of about 8-10 cm/year in a dose of 0.5 IU/kg/wk(6-8). Another recombinant growth hormone without the methionyl residue has also been developed(9). Clinical trials showed that the gain in height was comparable and the preparation was less antigenic than Met-GH(9,10).

Growth hormone has rarely been used in India to treat children with short stature secondary to GHD(11). Twenty children with GHD who received short term therapy with recombinant GH for a period of 12 months at AIIMS, New Delhi had a height gain of about 8.0 ± 2.21 cm/yr with-

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out any adverse effects(12). The major handicap for pediatricians and endocrinologists in most developing countries is the non-availability and the prohibitive cost of these preparations. The current cost of growth hormone treatment for a 20 kg child is about Rs. 1,00,000 per year (1 IU = Rs. 225-270). The drug is exempted from customs duty but is still not marketed in India.

Factors Affecting GH Therapy

The effects of GH are dependent upon the stature, the pretreatment growth velocity, the GH secretory status, the dosage used and the route of administration of GH. Children growing faster need a larger dose of GH to achieve similar acceleration. The regimen with increased frequency of administration (6-7 per week) is better than the conventional 2-3 per week regimen.

The benefits of GH treatment in GHD are substantial. The response is most pronounced in the first year of treatment to about 8-10 cm/year. Both bone age and growth advance proportionately. The initial acceleration of growth velocity is positively correlated with the extent of deviation from normal at the time of treatment.

Long Term Auxologic Effects

A 5-year follow-up study from Turkey showed that height standard deviation score (SDS) for chronologic age increased significantly throughout all treatment years but the height SDS for bone age did not change either in prepubertal or pubertal children(13). GH therapy prevents thus further loss of stature but cannot make up the loss of height already present at the time of diagnosis. This underlines the importance for early referral and treatment. Approximately 50% of the children with idiopathic GHD given GH therapy achieve normal adult height(14,15). The final height positively correlates with midparental height and negatively with degree of departure from normal at the time of treatment. The failure to achieve the potential could be due to a variety of factors such as noncompliance, early puberty, inadequate dose, late diagnosis and limited availability. Approximately 10% of the children do not respond to GH treatment. Children with multiple pituitary hormone deficiency (MPHD) especially deficient gonadotropin secretion tend to have better final adult height(16).

Adverse Effects of GH Therapy

There are very few reports of the adverse effects of GH therapy. Local abscesses and lipodystrophy are very rare. Slipping of the capital epiphysis of the femur has been reported in earlier years of human GH therapy. The reason for this appears to be the instability of the epiphysis during rapid growth. It is less common now.

The major concern has, however, been the formation of *antibodies*. Antibody formation was a common problem with earlier preparations but is not a major one with the current monomeric GH preparations. However, the most important question is whether these antibodies are *growth attenuating* or not. This appears to be dependent on the quality and quantity of antibodies(17,18). Growth attenuating antibodies against pituitary derived GH appears to be exclusively seen in patients with genetic forms of GHD. Changing to a purer form of GH may be helpful to restore growth in them. Antibodies are present in significant titres after 6 weeks of treatment with recombinant GH and are maximum after 6

months(6,18). It is also argued that the antibodies prolong the presence of GH in circulation and this would have potential benefit for the growth of the child.

GH therapy has not produced signs and symptoms of acromegaly in any children so far. *Diabetogenic effects* such as overt glucose intolerance are exceedingly uncommon with the currently used doses of GH. Diabetic responses to glucose tolerance tests are found in some children receiving doses of GH more than 5 IU/day.

Hypothyroidism is often apparent after GH therapy is started(19). About 30 per cent of children require initial l-thyroxine or increase in dose of l-thyroxine due to "unmasking" of "accentuation" of hypothyroidism. Recombinant GH treatment induces a positive nitrogen balance, however no serious *renal* side effects are reported.

Long term adverse effects of GH therapy in these children are unknown(20). The risk of an increase in leukemia or malignancy associated with GH therapy is small, if it existed at all(21).

Predictors of Response to GH

The final adult height obtained with GH therapy is related to the target height, usually below it, but is not determined by chronological or bone ages, bone age delay, height velocity before or during therapy nor by duration of treatment(22). A subsequent study showed that the children with the slowest pretreatment height velocity showed the best increment(23). An inverse relation was found between the endogenous GH secretion and increment in growth(23,24). The basal levels of IGF-1 or IGF-2 were not good predictors in these studies. A better response was related to lower baseline IGF-1 concentration and lower height age, but post-treatment levels were not(25). The final answer to prediction of which child will benefit best from GH therapy is still elusive and calls for careful professional anthropometry(3).

GH for Short Stature other than GHD

Short children with a predicted adult height below the 3rd centile but with normal response to physiological or pharmacological stimuli also have been found to respond to GH therapy(15,26). Many of these children are now reclassified as *GH neurosecretory dysfunction* based on 24 hour GH profile and IGF-1 levels(27).

Turner syndrome with short stature also responds to treatment with GH either alone or in combination with oxandrolone. In general, combination therapy seems to be better than either drug alone. The conditions in which GH therapy appears to be helpful include growth failure secondary to uremia and chronic renal failure(29), chemo- and radiotherapy for leukemia(30), constitutional delay of growth and adolescence(31) and intrauterine growth retardation. The list is increasing as years go by.

It appears GH deficient adults have impaired self-esteem and related symptoms and GH therapy improves their psychological and physical well-being. The lean body mass increases especially in the first months with an overall decrease in fat mass with no significant change in body weight(33).

Aging is related to diminished GH secretion and it is believed that administration of GH will reverse or retard certain aspects of aging process(34). The potential of GH in improving nitrogen balance and wound healing is under investigation(35).

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