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Treatment of Idiopathic Short Stature with Growth Hormone

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Fifty years ago, treatment of growth hormone deficiency with human growth hormone (hGH) was first reported by Raben from the Tufts Medical Center[1]. In the early years each pituitary supplied enough growth hormone for treating one child for one week. Thus the hormone available for therapy was very scarce. For the next 25 years demands far exceeded supplies and treatment was limited to severely affected children. In 1981 we reported a growth hormone deficient boy who developed a rare neurological disorder and postulated that the disease (presumed to be Creutzfeldt-Jacob) was transmitted by a "slow virus" (now called prion) via the administered pituitary derived growth hormone[2]. Other reports soon followed and four years later treatment with hGH was banned worldwide.

Biosynthetic growth hormone (GH) has an aminoacid sequence identical to hGH and is made by bacteria or other cells using recombinant DNA technology. In the United States, the Food and Drug Administration (FDA) licensed biosynthetic growth hormone (GH) for treatment of growth hormone deficiency in 1985 and the drug received regulatory approval in other countries shortly thereafter. With the availability of a virtually limitless supply of biosynthetic growth hormone the therapeutic indications for GH use gradually increased over the following years (Table 1).

Table 1. The Food and Drug Administration (USA) approved indications for growth hormone (somatropin) therapy

Disorder	Year
Growth hormone deficiency (children)	1985
Chronic renal insufficiency	1993
Turner syndrome	1996
AIDS wasting	1996
Adult growth hormone deficiency	1996
Prader-Willi syndrome	2000
Small for gestational age	2001
Idiopathic short stature	2003
Noonan syndrome	2007

There are no well established criteria for the diagnosis of idiopathic short stature (ISS). In the absence of any specific clinical findings or diagnostic laboratory tests, ISS is generally defined as exclusion of genetic, endocrine, and other contributory factors in an otherwise normal short child. Thus children with ISS are a heterogeneous group of patients and often include children born small

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for gestational age (intra-uterine growth retardation) and the so-called familial short stature. Furthermore what constitutes shortness is subject to controversy. Depending on the social and cultural mores children whose heights fall below the 5th or 3rd percentile lines, or those who are three standard deviations (SD) below the mean might be referred for consideration for GH therapy.

Treatment of children with ISS with GH is controversial. There also is no unanimity as to which children should be treated. Nonetheless GH therapy has received regulatory approval for this indication in the United States and other countries. The FDA has approved GH for children with ISS whose height is on or below the 1.2 percentile line (-2.25 SD).

The approval was based on a study of 68 children treated with either GH or placebo. The therapeutic efficacy was judged by comparing the growth rate of treated children with that of the placebo group. The near final heights of the subjects were also compared with their predicted adult height. GH treated patients had an acceleration of growth rate and a mean of 3.7 cm increase in their final height.[3] The near final height was 5 cm more than the predicted adult height in 60% of the treated children. Using larger doses of GH, subsequent studies have shown better outcomes[4]. Short-term studies suggest that treatment with analogs of gonadotropin releasing hormone (GnRH) or with aromatase inhibitors may enhance the final height. However long-term results of combination therapy with either GH and GnRH or GH and aromatase inhibitors are still not available. It is also not known whether an increase in final height results in improved quality of life and psychosocial well-being.

Growth hormone is generally thought to be a safe medication. Several relatively minor clinical and laboratory abnormalities have been associated with the use of GH, however these have not impacted the therapeutic decision to any appreciable degree. Major undesirable effects are rare. Benign intracranial hypertension (pseudotumor cerebri) and slipped capital femoral epiphyses each occur in about 1:700 patients. Over twenty years ago a report from Japan suggested a doubling incidence of leukemia in GH treated children[5]. Subsequent large epidemiologic studies in various countries including Japan, have failed to confirm an increased risk. More recently, in a review of 1844 patients who had been treated with hGH, there were two deaths from colon cancer and two others from Hodgkins disease.[6] However a cause and effect relationship could not be established. Nonetheless increased risk of malignancy, especially in children who have other risk factors, continues to be a concern. Several studies have suggested an association between increased cancer risk and a combination of high insulin-like growth factor-1 (IGF-1) and low IGF-1-binding protein-3 concentrations. It is therefore prudent to monitor IGF-1 and IGF-1 BP-3 levels in patients who are receiving long term GH therapy.

Even though the price of growth hormone varies in different countries, it is expensive everywhere. The estimated cost of ISS treatment in the U.S is $20,000 per cm increment in the final height. The cost per cm of additional height elsewhere in the world is similarly high. It has been argued that the acceleration of growth rate at a time when the child is most vulnerable, justifies treatment even if the final height is not significantly altered. A child whose height is on or below the 3rd. percentile line (almost 2 SD below the mean), or 1.2 percentile line is clearly short. However commitment to treating such children would entail treatment of 3% (or 1.2%) of normal population and drainage of badly needed health monies for what many perceive as a social, and not a medical, problem. With these limitations in mind, perhaps only ISS children with heights 3 SD or more below the mean (about 1/2000) should be considered for GH therapy.

The initiation or withholding of growth hormone therapy for ISS has medical, legal,

ethical, economic and psychosocial implications. The regulatory approval of GH therapy has created a dilemma for payers, parents and endocrinologists. Clearly the parents and physicians must decide individually for each child whether to treat or not. In each patient the potential undesirable psychosocial impact of short stature must be weighed against the risks of giving the child the feeling that he/she is not acceptable to the parents, setting unrealistic growth expectations, discomfort of daily injections, risks of side-effects, and the financial burden to parents and the society at large. In managing these patients we must help the parents and the society at large determine whether idiopathic short stature is a disease to be treated medically or a social problem that can be overcome with family support and less costly and noninvasive means.

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