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Endocrinología pediátrica

Growth hormone in idiopathic short stature(ISS). Safety and efficacy data

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Children with ISS have a growth disorder of currently unknown and likely heterogeneous etiology. Short stature in ISS is of similar severity to other growth disorders (eg GH defic, GHD and Turner Syndrome, TS). The FDA approved in 2003 GH for ISS at a dose of 0.37 mg/kg/wk. ISS was defined as a height of -2.25 SDS and it is associated with growth rates unlikely to permit the attainment of adult height in the normal range. Of more than 40 studies conducted with regard to GH in ISS three large studies will be reviewed in this overview.

1. US Multicenter Study (Genentech). The study showed that GH improved height from -2.7 SDS at baseline to close to -1.0 at final height after 7 yrs of treatment the gain was 5.7-9.1 cm compared to untreated controls of -2 SDS heights. GH dose 0.3 mg/kg/wk, daily.

2. Placebo controlled US study (Eli Lilly). GH effect was 0.5 SDS or 3.7-5.0 cm gain, compared to placebo group. Subjects were already peripubertal at baseline GH dose was modest at 0.22 mg/kg/wk, given three times/week.

3. Dose response study (Eli Lilly). GH dose of 0.37 mg/kg/wk gives 3 cm greater final height gain in patients on high dose group compared to low dose group receiving 0.24 mg/kg/wk daily. Children were all prepubertal. Height gain 5.4-7.3 cm vs baseline predicted height, 82% of final height patients in high dose group gained at least 1 SDS in height, 62% gained more than 5 cm, 31% gained more than 10 cm, 94% of final heights in the high dose group were in the normal range.

4. Two recently published analyses (Genentech and Eli Lilly) of the safety of GH in ISS (JCEM September 2005) come to similar conclusions: long-term GH therapy (up to seven yrs) is safe and effective in children with ISS and that the outcomes with regard to efficacy and safety can be expected to be comparable with that reported in formal clinical trials.

Longer term data are still necessary given the potentially long life span of children.

5. A major initial concern was that GH therapy might lead to impaired carbohydrate intolerance in these children, particularly in children with who are SGA (small for gestational infants) and are saddled with *A priori* potential hyperinsulinism as early as adolescence. In a recent study we found that GH treatment at a dose of 0.48 mg/kg/week for one year had no deleterious effects on glucose tolerance. The children had higher insulin levels at one year. This rise was however not clinically significant and reverts promptly to baseline after GH administration is discontinued.

6. The challenge is now to find a molecular basis for idiopathic short stature. While some may simply suffer from constitutional delay of growth and development (delayed puberty) others may have low IGF-1 levels despite normal GH levels. These children may have mutations/deletions of the GH receptor gene impairing GH binding or causing an inability to initiate the signal cascade leading to a normal IGF production. (STAT 5b mutations), deletions or mutations of the IGF-1 gene, and finally mutations of the gene for the acid-labile subunit (ALS), part of the ternary complex responsible for IGF transport in serum. In deconstruction the potential causes of ISS, endocrinologists will lay the foundations towards a molecular basis of ISS.

In conclusion: the therapeutic efficacy of GH in ISS is similar to GHD and TS. No new safety concerns were seen in this population. There was no evidence of accelerated bone age maturation and IGF-1 levels rose in the first year of treatment to high normal levels with a gradual decline towards mean levels in subsequent years. There was no evidence for carbohydrate intolerance. Given the long life span of children continued vigilance is however necessary.