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CLINICAL

Growth hormone for short children – whom should we be treating and why?

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TITLE Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review

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DECLARATION OF INTERESTS Professor Kelnar receives honoraria for speaking at meetings sponsored by, and has in the past received research grants from, growth hormone manufacturers. He has also been a member of advisory boards for growth hormone manufacturers.

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SUMMARY

The objective of this paper was to determine systematically the impact of growth hormone (GH) therapy on adult height of children with (so-called) 'idiopathic short stature' (ISS) using the Cochrane Central Register of Controlled Trials, Medline, and the bibliographic references from retrieved articles of randomised controlled trials (RCTs) and non-RCTs from 1985 to April 2010. Inclusion criteria were initial short stature (defined as height >2 standard deviation [SD] below the mean), peak growth hormone responses >10 micrograms per litre (µg/L), prepuberty, no previous growth hormone therapy, and no comorbid conditions that would impair growth. Data extracted were adult height and overall gain in height from baseline measurement in childhood.

Three RCTs (115 children) met the inclusion criteria. The adult height of the GH treated children exceeded that of the controls by 0.65 SD score (~4 cm). The mean height gain in treated children was 1.2 SD score compared with 0.34 SD score in untreated children. A difference of ~1.2 cm in adult height was observed between two GH dose regimens. In the seven non-RCTs, adult height of the GH-treated group exceeded that of controls by 0.45 SD score (~3 cm).

The authors conclude that 1) GH therapy in children with ISS seems effective in partially reducing the deficit in height as adults, although less so than in other conditions for which GH is licensed; treated individuals remain relatively short compared with normal height peers. 2) Individual responses to therapy are highly variable; further studies are needed to identify responders. 3) High quality evidence from long-term RCTs of GH therapy that continue until adult height is necessary to determine the ideal dosage and long-term safety.

OPINION

Short stature is not a disease and 'normal' is not 'average'. Making someone taller, even if achievable, is not an end in itself. While GH therapy for clearly GH-deficient short children is well accepted, treatment of ISS remains controversial.[1,2] However 'normality', 'GH insufficiency', and 'ISS' remain difficult to define due to the poor efficiency, sensitivity and specificity of GH stimulation tests. Because something is measurable, or is thought to be (e.g. a GH level in response to a particular stimulation test) does not render the outcomes clinically relevant.[3,4] Equally, adult height is not a validated proxy for psychological contentment or 'quality of life' (QoL). Sometimes what is most important is most difficult to measure.

Statistically significant outcomes, e.g. (slightly) increased adult height, must be evaluated in terms of clinical benefit – the presence and potential for alleviation of short stature-related distress is crucial.[5] Many pronouncements relating to the psychosocial consequences of short stature are based on children referred for investigation, who are more likely to have other pathology or greater problems with psychosocial adaptation (or parents who perceive that they will). Evidence suggests little effect on psychological functioning from being shorter than average in children, adolescents or adults.[6–8]

Studies on the pharmacological use of GH in ISS must be designed not simply to determine the most effective strategy to improve adult height, but also to balance the effect of height gain on psychological health and social wellbeing against effects on QoL of daily injections, potential short- and long-term adverse effects of GH therapy (including unmet expectations) and treatment costs. Long-term safety data (including in adults treated with GH in childhood only) are necessary.

Clinical medicine is a holistic attempt to provide the best care for patients.[9] A clinician's knowledge may be biased (belief versus knowledge), families' and patients' expectations may be unrealistic, and a 'worthwhile' outcome may be difficult to define.[10–12] Unless broader questions are raised as to what constitutes benefit,[6] the debate in treating short children will remain at the 'centimetres gained' (or even 'predicted to be gained') level, and properly designed studies to address important wider safety issues and psychological and QoL outcomes will not take place.

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