

Advent of recombinant human growth hormone to increase final adult height of the normal child

Introduction

This commentary is motivated by the publication of the Briefing Document on the use of somatropin for non-growth hormone deficiency short stature by Eli Lilly on 1 May 2003. This was followed by approval by the US Food and Drug Administration's (FDA's) Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 10 June 2003, and subsequent full approval by the FDA on 25 July 2003. Eli Lilly has advised the FDA that it will not engage in direct-to-consumer advertising of somatropin, and will limit the marketing of the new use of this product to paediatric endocrinologists in order to better ensure the proper use of this product in the indicated population. In addition, the manufacturer intends to tightly control its distribution.¹

Use of somatropin

Recombinant human growth hormone (rhGH), somatropin, identical in amino acid sequence to native human growth hormone (GH), was approved in 1987 by the FDA.¹ Safety and ethical issues have dominated the debate over the cosmetic use of synthetic rhGH for short but normal children ever since its introduction in 1985 as a product with limitless supply. Prior to the 2003 landmark decision, FDA approval for use of rhGH in paediatric patients was limited to children with endogenous growth hormone deficiency (GHD) and Turner syndrome. The Danish Consensus Guideline of July 2000 widened its use to include growth failure associated with chronic renal insufficiency. However, it queried its use in very short, slowly growing GH sufficient children whose height was more than two standard deviations (SD) below the mean, due to inaccuracies in height prediction methods.² As recently as 1997, Brook wrote in a *British Medical Journal* editorial that "the treatment of short, normal patients in the mistaken belief that treatment [with rhGH] could improve final height is a cruel and expensive mistake" and further opined that there were insufficient "hard psychological endpoints to test the hypothesis that the increase in growth rate which growth hormone treatment will achieve in short children would be beneficial".³ These comments were made while reminding readers that almost any child given GH in sufficient doses will grow more quickly, and that dose-response curves for human GH treatment have been available for some years.⁴ An original study on this issue concluded that from the perspective of the endpoint achieved, treatment started earliest achieved the best results.⁵

Now, the FDA has concluded that rhGH is effective in

increasing the final height of children with non-GHD short stature with a height of no more than 2.25 SD below the mean for their age and sex. This approval is likely to trigger a worldwide explosion in demand for somatropin by parents who would like their children to be taller, irrespective of whether there is short stature. In affluent Hong Kong, we should be considering this issue now in anticipation. In the US, 'off label' use of rhGH for children with non-GHD short stature by physicians has been evident for many years. The FDA has not included this indication in its list of approved uses, but doctors are not prohibited from using it for this purpose.

Safety

With an estimated 100 000 patients worldwide having received GH treatment since 1985, safety aspects have always been a concern. Given the anticipated increase in use, continuing vigilance is mandatory. The role of GH treatment in carcinogenesis remains unclear, but it is known to raise serum concentrations of insulin-like growth factor, IGF-1, which is mitogenic and anti-apoptotic, theoretically increasing the risk of hyperplasia and malignancy.⁶ A cohort study to investigate cancer incidence and mortality in 1848 patients treated during childhood between 1959 and 1985 in the UK, concluded that the data did not show conclusively whether cancer incidence was increased by GH treatment after exclusion of patients whose original diagnosis rendered them at high risk of cancer. The caveat was that there might be a small increase in the risk of colon cancer and Hodgkin's Disease but that this finding may be flawed because of the small sample size.⁷

Although consensus studies on GH treatment safety suggest an acceptable overall safety profile in terms of carcinogenesis,^{2,8} it would be prudent to be vigilant of known side-effects of GH, such as benign intracranial hypertension, which is reported in 1/1000 children receiving GH treatment,⁸ and to avoid its use in the presence of tumour activity.² In the absence of other risk factors, there is no evidence of significant risk of leukaemia, brain tumour recurrence, slipped capital femoral epiphysis, or diabetes in recipients of long-term GH treatment.^{2,8}

Basis of United States Food and Drug Administration's approval

The question of whether rhGH is effective for children with non-GHD short stature is clouded by the problem that most studies have compared final height with predicted height—an inherently imprecise estimation.⁹

The FDA EMDAC's 10 June 2003 landmark approval¹ was based on three main considerations:

- (1) The pivotal study carried out by Eli Lilly and the National Institute of Child Health and Human Development, coded B9R-MC-GDCH, was a randomised, double-blind, parallel, placebo-controlled study that assessed final height in paediatric patients with non-GHD short stature (n=71). The original protocol defined the criterion for protocol completion as the achievement of a height velocity of less than 0.5 cm/year. This criterion was later changed to address the issue of 'drop-outs' that occur as the height gain velocity slows down upon the approach to final height. Understandably, with this more limited progress, the patient is less likely to continue injections and more likely to drop out of the study. The dosage of rhGH used in the study was 0.22 mg/kg/week, administered in divided doses three times a week. At this dosage, there was a real but relatively small increase in growth of only 3.7 cm (1.5 inches).
- (2) The supportive study, coded B9R-EW-E001, was conducted in 10 European countries. It was an open-label, three-arm, randomised, parallel, dose-response study. Paediatric patients with non-GHD short stature (n=239) were randomly assigned to receive different dosages, in divided doses given six times per week. The core study was conducted over a period of 2 years. At the highest dosage used of 0.37 mg/kg/week, the growth increase was 7.2 cm (+/- 1.7 cm).
- (3) The 2002 meta-analysis by Finkelstein et al¹⁰ summarised 10 peer-reviewed, controlled studies and 28 uncontrolled studies that used rhGH from several manufacturers. It concluded that rhGH-treated patients with non-GHD short stature demonstrated an average of GH-induced gain in adult height of approximately 4 to 6 cm.

Discussion

From the perspective of health economics, government funding of this expensive, non-fatal, and long-term treatment should be given low priority. With Hong Kong's current huge government fiscal deficit, such a new treatment is likely to come under the closest scrutiny however effective.

Clinically, before any child is considered for rhGH therapy, meticulous documentation of accurate and frequent height measurements on a proper stadiometer is paramount. Data should never be massaged to fit the child into this prolonged treatment. Furthermore, where the epiphyses have closed, rhGH treatment has no benefit, and parents and their children need to be advised of this sympathetically, but firmly.

From the perspective of the individual, children with non-GHD short stature are equally as deserving of treatment

as those with short stature due to Turner syndrome or Prader-Willi syndrome, chronic renal failure or children born small for gestational age. The absence of hard evidence showing any psychological or social benefit from an increase in physical stature is unlikely to sway the views of determined parents. For now, the remaining barrier is probably the cost, varying anywhere from US\$10 000 to US\$40 000 a year, depending on dosage, age, height, and weight. The bothersome requirement of daily injections is practically resolved with the latest needle-less injectors.

Where there is significant constitutional delay in growth and sexual maturity, evidenced by marked delay of bone age to chronological age, judicious use of sex hormone of appropriate duration and dosage is effective and safe to bring forward the onset of the growth spurt.¹¹ This should be a consideration confined to the highly specialised realm of the paediatric endocrinologist, particularly since treatment is unnecessary in many cases.

The plight of children with short stature in a society that is bent on admiring those with tall stature and Olympian physique will remain difficult to quantify in scientific terms. Taking into account the different ethnicity of children, common sense would suggest short children born into a population of different stature would expect to find themselves treated differently. The problem of course does not stem from the short child, but the lack of compassion and understanding from peers of taller stature. Some would recommend simply that the short child adapt, acquire coping skills,³ and to rectify height prejudice through education.⁹ Now with proven medical assistance available to increase final adult height in non-GHD short stature, this is the opportune moment to instead consider increasing the stature of the short child.

Armed with the knowledge that rhGH use is relatively safe and effective for children with non-GHD short stature, the decision on whether or not to use rhGH in such children is arguably the prerogative of the parents and child concerned, not society.

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Answers to CME Programme *Hong Kong Medical Journal* October 2003 issue

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I. Management of febrile convulsion: scene in a regional hospital

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| A | 1. True | 2. False | 3. False | 4. True | 5. False |
| B | 1. True | 2. True | 3. False | 4. False | 5. True |

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II. Sudden cardiac death: prevention and treatment

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| B | 1. False | 2. True | 3. True | 4. False | 5. True |