Growth hormone in children

Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Recombinant growth hormone (GH) is licensed for use in children with GH deficiency (GHD), Turner syndrome (TS), chronic renal failure (CRF) and Prader–Willi syndrome (PWS). GH is also used in conditions for which it is not licensed, such as idiopathic short stature (ISS).

In all five of these indications for GH treatment, affected children, if left untreated, can be about 12–36 cm (5–14 inches) shorter than the normal mean height as adults. The primary rationale for prescribing GH to children is to improve their short-term growth and/or their final height.

Epidemiology

Prevalence estimates suggest that, in England and Wales, there are approximately 28,500 children between the ages of 0 and 16 years who are affected with the conditions of interest (approximately 2900 children with GHD, 1970 with TS, 640 with CRF, 540 with PWS, and 22,450 with ISS). Only about 7% are currently being treated (approximately 2000 children), the majority (78%) having GHD, CRF or TS.

Objectives

This review considers the clinical effectiveness and cost-effectiveness of GH therapy in children with GHD, TS, CRF, PWS or ISS.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

The main electronic databases were searched, with English language limits, for the periods up to April 2001. Bibliographies of related papers were assessed for relevant studies, and experts were contacted for advice and peer review, as well as to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Clinical Excellence were reviewed.

Study selection

Studies were included if they fulfilled the following criteria, which were applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

- Intervention was biosynthetic human GH (somatropin).
- Participants were children with one of five conditions: GHD, TS, CRF, PWS or ISS.
- Outcomes were final height and short-term growth responses to treatment, such as height standard deviation score and height velocity. Quality-of-life measures were reported if available.
- Designs were randomised controlled trials (RCTs) or systematic reviews of RCTs that assessed the effects of GH (compared with placebo or no intervention) based on any of the above patient-relevant outcomes. If final height was not an outcome in at least one of the RCTs for that condition, the best studies from lower down the hierarchy of evidence that reported final height were included. Economic evaluations of GH in children suffering from one of the five conditions were included in the review of cost-effectiveness if they included a comparator (or placebo) as well as both the costs and consequences (outcomes).

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of RCTs was assessed using Jadad criteria, and non-RCTs were assessed using modified Spitzer criteria. The internal validity of economic evaluations was assessed using the *BMJ* checklist, and external validity was assessed using a series of relevant questions.

Data synthesis

The clinical effectiveness of GH in children was synthesised through a narrative review with full tabulation of results of all included studies. In the economic evaluation, a cost-effectiveness model was constructed using the best available evidence to determine cost-effectiveness in a UK setting.

Results

Number and quality of studies

RCTs comparing GH with placebo or no treatment were included, and because final height data were rarely available in the context of RCTs, lower levels of evidence were included for final height only, using the highest level of evidence available within each condition. A total of 34 publications reporting 32 studies were included in the assessment of clinical effectiveness. Short-term growth and final height outcomes were evaluated along with some body composition and psychological outcomes. The Jadad quality scores of the trials ranged from 1/5 to 4/5.

No existing economic evaluations were found, nor were there any studies reporting appropriate measures of quality of life.

Summary of benefits

Although the quality of evidence proved variable, the studies suggest that GH treatment can increase short-term growth and improve final height. The reported effects of GH on short-term growth should be considered more reliable because the evidence is of higher quality. The effects of GH on final height should be considered with much greater caution because the quality of the studies is generally much poorer.

Results suggest that the effects of GH on short-term growth velocity (at 1 year) can range from no improvement to approximately 1 standard deviation above the normal growth velocity for children of the same age.

Final height gains for treated children over untreated children appear to range from approximately 2 to 11 cm (GHD, 8–11 cm; TS, 5 cm; CRF, 3–9 cm; PWS, 10–11 cm; ISS, 2–7 cm).

Costs

Treatment with GH is expensive. The lifetime incremental cost of treating one child with GH (as opposed to simply monitoring growth) ranges from £43,100–53,400 (for GHD) to £55,500–83,000 (for PWS). These costs, when applied to children aged 8–15 years with the analysed indications in England and Wales, result in total discounted costs of £904 million for complete treatment. The costs for treating children only in the four licensed conditions would be approximately £180 million.

Cost per centimetre gained

The available data suggest that, under base case conditions, the incremental cost per centimetre gained in final height is approximately £6000 for GHD, £16,000–17,400 for TS, £7400–24,100 for CRF, £13,500–27,200 for ISS and possibly in the region of £7030 for PWS (estimated using year 2000 prices).

Sensitivity analysis

A range of impacts of parameter values for the economic models were evaluated in sensitivity analyses. These evaluations tested length of treatment (1–13 years), final height effect (10–300% of the effect from the base case from trials), GH dose (varying by indication), GH cost (£15– 25/mg), annual range of discounting for benefit (0–6%) and annual rate of discounting costs (0–12%). The analyses confirmed the sensitivity of cost-effectiveness estimates and the most important factors (effectiveness, GH dose and costs due to the length of treatment).

Limitations of the calculations (assumptions made)

The economic evaluation is limited by the quality of the trials that provided the effectiveness data. In addition, these trials may not be generalisable to current treatment programs because even those that continued to final height generally started with relatively old children and treated them for a relatively short time (approximately 5–8 years). These factors were evaluated in the sensitivity analyses, but which combinations of conditions could actually exist needs careful consideration.

Conclusions

Implications

GH is already prescribed in the UK. However, a full course of treatment is expensive. Given that only a minority of children with licensed conditions are currently receiving GH, the budgetary impact of large increases in prescribing would be substantial. If GH were to be prescribed to any significant proportion of children with ISS, the budgetary impact would be very substantial because this group of children is much larger than the others.

Need for further research

Large, multicentre RCTs are needed. These RCTs should focus on final height, which is the best outcome for assessing the effectiveness of GH, and should address quality-of-life factors for use in economic modelling.

Publication

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