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Recombinant growth hormone for idiopathic short stature in children and adolescents (Review)

Bryant J, Baxter L, Cave CB, Milne R

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[Intervention Review]

Recombinant growth hormone for idiopathic short stature in children and adolescents

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ABSTRACT

Background

Idiopathic short stature (ISS) refers to children who are very short compared with their peers for unknown or hereditary reasons. Recombinant human growth hormone (GH) has been used to increase growth and final height in children with ISS.

Objectives

To assess the effects of recombinant human GH on short-term growth and final height in children with ISS.

Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE, *The Cochrane Library*, Science Citation Index, BIOSIS and Current Controlled Trials. Article reference lists were assessed for trials and experts and pharmaceutical companies were contacted.

Selection criteria

Randomised controlled trials were included if they were carried out in children with ISS with normal GH secretion. GH had to be administered for a minimum of six months and be compared with placebo or no treatment. A growth or height outcome measure had to be assessed.

Data collection and analysis

Two reviewers assessed studies for inclusion criteria and for methodological quality. Data were extracted by one reviewer and checked by a second. The primary outcome was final height and secondary outcomes included short term growth, health related quality of life and adverse effects. To estimate summary treatment effects, data were pooled, when appropriate using a random effects model.

Main results

Ten RCTs were included. One trial reported near final height in girls and found that girls treated with GH were 7.5 cm taller than untreated controls (GH group, 155.3 cm ± 6.4; control, 147.8 cm ± 2.6; P = 0.003); another trial which reported adult height standard deviation score found that children treated with GH were 3.7 cm taller than children in a placebo-treated group (95% confidence intervals 0.03 to 1.10; P < 0.04). The other trials reported short term outcomes. Results suggest that short-term height gains can range from none to approximately 0.7 SD over one year. One study reported health related quality of life and showed no significant improvement in GH treated children compared with those in the control group, whilst another found no significant evidence that GH treatment impacts psychological adaptation or self-perception in children with ISS. No serious adverse effects of treatment were reported.

Authors' conclusions

GH therapy can increase short-term growth and improve (near) final height. Increases in height are such that treated individuals remain relatively short when compared with peers of normal stature. Large, multicentre RCTs are required which should focus on final height and address quality of life and cost issues.

PLAIN LANGUAGE SUMMARY

Recombinant growth hormone for idiopathic short stature in children and adolescents

There is some evidence that recombinant human growth hormone improves short term growth and (near) final adult height in children with idiopathic short stature.

Idiopathic short stature is the term used when children are very short compared with others of their age for unknown or hereditary reasons. They do not have a disease. Recombinant human growth hormone has been used to try to overcome growth failure in these children. It must be injected under the skin six to seven times a week until adult height is reached. Existing evidence suggests that growth hormone can increase short term growth and improve final or near final adult height.

Ten studies included altogether 741 children and lasted between six months and 6.2 years. Results showed that individuals treated with growth hormone remain relatively short when compared with peers of normal stature. Girls treated with growth hormone were 7.5 cm taller than untreated controls (growth hormone treated group 155.3 cm and control group 147.8 cm); another trial found that children treated with growth hormone were 3.7 cm taller than children in a placebo-treated group. No serious adverse effects were reported in the included studies. Although serious adverse effects (there has been concern that growth hormone would induce new tumours or increase the likelihood of tumour relapse) may be rare, their possibility must also be taken into consideration.

BACKGROUND

Description of the condition

Idiopathic short stature is the term used when children are very short compared with others in their age cohort for unknown or hereditary reasons. By definition, children with ISS do not have a disease.

Idiopathic short stature is commonly defined as height below the third percentile or about two standard deviations (SD) or more below the mean height for a given age, sex and population group. Approximate untreated adult height (in cm) for males with ISS ranges from 157 cm to 170 cm, compared with a mean of 178 cm for normal males (2 SD below the mean being 164 cm); untreated adult height for females with ISS ranges from 137 cm to 156 cm, compared with a mean of 164 cm for normal females (2 SD below the mean being 152 cm) (Price 1996; Preece 2000).

Characteristics of idiopathic short stature

Children with ISS are a heterogeneous group, made up of individuals whose short stature cannot be explained by an underlying pathology and who meet the following minimal criteria (Ranke 1996):

- normal size for gestational age at birth;
- normal body proportions;
- no evidence of endocrine deficiency;
- no evidence of chronic organic disease, no psychiatric disease or severe emotional disturbance, and normal food intake;
- the growth velocity throughout the growth process may be slow or normal.

Recombinant human growth hormone has been used to increase growth and final height in ISS.

Incidence and prevalence of idiopathic short stature

Precise estimates for incidence and prevalence of ISS are difficult to obtain. ISS is not determined by diagnostic criteria as it is not a disease and is generally defined by a combination of factors. Children who may be prescribed growth hormone on the basis of ISS generally meet at least two criteria. First, children must be below the third percentile of height and in addition, they must be growing slowly. It is difficult to estimate how many of the lowest 3% of children in height might actually be prescribed growth

hormone. One study evaluated children below the 3rd percentile for height and found that only 5% did not reach an adult height greater than two SD below the mean (Ranke 1995). Another study found that 9% of very short children might be prescribed growth hormone (Finkelstein 1998). Therefore, between 5% and 9% of the shortest 3% of the population could be recommended for growth hormone treatment, which is about 0.2% of the child population.

Description of the intervention

Recombinant human growth hormone has been available since 1985, shortly after growth hormone from cadaveric human pituitaries was withdrawn from use because of its association with the transmission of Creutzfeldt-Jacob disease (Taback 1999). Recombinant human growth hormone (somatropin) is produced by recombinant DNA technology and has a sequence identical to that of human growth hormone. Somatropin is available from several manufacturers under different brand names. The advent of recombinant GH has meant that GH is far more available and GH has been widely used to treat various growth disorders including ISS (Gault 2001), although it is not licensed in the UK for treatment of children with ISS.

The number of children with ISS being treated has not been separated from other unlicensed indications, but it has been estimated that at most approximately 275 children with ISS may be receiving treatment in the UK (Hilken 2001). GH is usually prescribed in association with a paediatric endocrinologist or a general paediatrician with a special interest in endocrinology. Routine follow-up should be performed by a paediatric endocrinologist in partnership with the general paediatrician and/or the general practitioner to assess the response to GH treatment. Treatment dosage will need to be amended as the child grows and at puberty. Consensus Guidelines have been produced by The British Society for Paediatric Endocrinology and Diabetes (Kirk 2001), which state that treatment should only be undertaken in specialist centres that regularly participate in national audit of their clinical activities, any potential benefits and adverse medical effects of therapy should be discussed fully with the parents and the child prior to treatment, and that response to treatment should be carefully monitored and the need for ongoing treatment should be re-evaluated annually.

Growth hormone is prescribed in milligrams (mg) or International Units (IU) according to body weight or body surface area and is self administered (or given by the parent) at home usually as a subcutaneous injection generally six to seven times per week. To more closely approximate the natural fluctuations in GH, the injections are usually given at night. In ISS where there is no GH insufficiency, GH is given at supraphysiological levels, levels considerably higher than normal, at 0.33 mg/kg/week (9-10 mg/m^2/week). The logic in administering supraphysiological doses is generally that children who have growth deficiencies, but not a hormone deficiency, may have some lack of sensitivity to the hormone (Kelnar 1999).

Growth hormone is generally prescribed for a number of years, from recognition of the growth deficit until growth is complete. For an individual child how long this would be will depend upon when the condition is identified. Most trials of GH have been of relatively short duration but in practice in many children therapy could continue for as long as 12 years or more. Expert opinion is that GH therapy should generally not be started before the age of four.

An aspect of considerable interest in the use of hGH in healthy children with ISS is to determine whether treatment with hGH affects children's sense of well-being or quality of life.

Adverse effects of the intervention

Growth hormone therapy is contraindicated in cases of tumour activity and should not be used for growth promotion in adolescents with closed epiphyses. Side effects can include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, paraesthesia, antibody formation, hypothyroidism and reactions at injection site. There has been concern that growth hormone would induce new tumours or increase the likelihood of tumour relapse. Reports suggest, however, that the risk of new tumours or tumour recurrence is not elevated in children treated with GH who have no other increased risk factor (Blethen 1996; Frisch 1997; GH Soc 2001).

Outcome measures used in assessing effects of growth hormone treatment

Height may be expressed in length units (for example cm) or in standard deviation scores (SDS). The standard deviation is a measure of the variation of observations around the mean. Heights of populations of adults or children generally form normal distributions such that 95.4% of a population will have heights that fall within 2 standard deviations from the mean. Individual observations can be compared with heights corresponding to points on the height distribution for a particular age to determine how a child's (or adult's) height compares with their peers. Standard deviation score is defined by the formula: actual height minus mean height for age divided by standard deviation of height for age. Standard deviation scores using controlled data collected from an appropriate population base allow comparison of measures independent of age or sex. In this system the normal population mean is zero and a normal SD score will lie between -2 and +2 SD. A healthy individual's SDS will not change during the growth years. Increased SDS implies catch-up growth and a decrease implies growth failure.

Height and growth can be considered either in terms of absolute values (for example final height = 160 cm) or in terms of change from a baseline value.

The best measure of how growth hormone affects growth is final height (in cm or SD). Measuring final height requires that the

child has finished growing. The most reliable measures of final height use multiple criteria to determine that growth is complete or nearly complete. Generally, it is considered that children have completed or nearly completed their growth, when their growth rate within a year has slowed to less than some specified amount (for example 1-2 cm) and skeletal maturity assessed by radiographs of the wrist and hand indicate that the epiphyses have closed (often expressed as bone age greater than a certain value, for example 14 - 15 years) (Frindik 1999). 'Near final height' may also be used acknowledging that growth may not be complete.

Although the overall effectiveness of GH in treating short stature is to be found in measures of final height, it has been argued that short-term measures of growth, such as growth velocity, are also of importance. Children and parents may be concerned with whether growth within a certain time frame is comparable to that of a child's peers. Growth velocity may also be a better interim growth measure than height attained at a particular age as it is independent of growth in previous years. Growth velocity is also used to assess the response of children to treatment (Child Growth 2000).

Growth velocity is a measure of the height gained (cm) within a specified time period (usually a year). This outcome is also often referred to as 'height velocity'. Growth velocity can also be considered in relation to a child's age by considering growth velocity relative to the distribution of growth velocities for children of a particular age (growth velocity standard deviation score). As with height, growth velocity SDS measures are dependent upon the reference data used (Child Growth 2000).

Bone age is a measure of skeletal maturity, usually determined by examining the relative positions of the bones in the left hand and wrist from a radiograph. Assessment of bone age is important to evaluate when the epiphyses have closed and growth is complete (growth cannot occur after the epiphyses [ends of the long bones] have closed).

Existing evidence on the use of growth hormone in idiopathic short stature

There is continued controversy over the use of growth hormone in ISS both in terms of how much additional height may be gained from treatment, and the ethics of treating children who do not have a disease (Allen 2006). Even with treatment, the final height of children with ISS may still be below the normal range. Also, although it may be of considerable value to increase the height of children who may be much shorter than their peers, there will always be children who make up the lowest percentiles on the height distribution curve.

There is a large volume of literature on the use of GH in ISS, ranging from RCTs to lower quality evidence such as case series. Evidence from high quality studies is to be preferred to reduce risk of biased results and to ensure apparent treatment effects are not artifacts of differences between patient groups.

Why it is important to do this review

Although there have been some reviews of the use of GH in ISS, (Wit 1996; Finkelstein 2002) there have been no reviews that have used systematic methods to locate and evaluate the best possible evidence.

OBJECTIVES

To assess the clinical effects of recombinant growth hormone on short-term growth and final height in children with idiopathic short stature.

This review has been published in part elsewhere (Bryant 2002).

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

Trial design

Randomised controlled trials or quasi-randomised trials were included. Trials had to evaluate one or more of the outcome measures described below.

Trial duration

For short-term outcomes, growth hormone (GH) had to be administered for a minimum of six months. For final height outcomes, GH had to be administered until final height is achieved. Criteria used within trials for final height were accepted (for example growth velocity less than 2 cm per year). Trials that reported 'near final' height were also included.

Types of participants

Participants were children with idiopathic short stature and with normal growth hormone secretion. A growth hormone level above 7µg/L (15 IU) following a stimulation test (for example by a provocative agent such as insulin and clonidine) defines normal growth hormone secretion.

Children with intra-uterine growth retardation were not included.

Types of interventions

The active intervention was GH, that is biosynthetic human growth hormone (somatropin), with a sequence identical to that of human growth hormone, marketed under any brand name.

- administration of GH for a minimum of six months versus administration of placebo.
- administration of GH for a minimum of six months versus no treatment.

Types of outcome measures

Outcomes focused on those that are clinically relevant to children with growth failure.

Primary outcomes

- Final height.

The gold standard outcome measure of effects of growth hormone treatment is final height (in cm or height standard deviation score [HtSDS] relative to a normal population).

Secondary outcomes

- short term growth. As most studies are of insufficient duration to report final height, short term growth responses to treatment were included, which may be reported as change in HtSDS over treatment period, growth velocity (change in cm per treatment interval (for example one year), or growth velocity standard deviation score;
- quality of life, ideally using a validated assessment instrument;
- adverse effects, such as benign intracranial hypertension, slipped capital epiphyses, effects on glucose metabolism and incidence of malignant disease;
- costs.

Exclusion criteria

RCTs that considered GH against another active treatment rather than placebo or no treatment were excluded. Dose-response trials which did not include a placebo or no treatment group were also excluded as they are not explanatory trials addressing the effects of GH. Trials that compared GH plus some other active treatment against only the active treatment were also excluded. In this type of design the effects of GH may be different than when GH is administered alone.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- *The Cochrane Library* (issue 4, 2005);
- MEDLINE (Ovid; 1981 to December 2005);
- PubMed (searched 7 June 2006);
- Science Citation Index (searched 7 June 2006);
- BIOSIS (searched 7 June 2006).

Searches were not conducted for trials before 1980 because recombinant growth hormone (GH) was not introduced until 1985. For details of the search strategy see Appendix 1.

On-going trials: National Research Register, Current Controlled Trials (www.controlled-trials.com; 7 June 2006).

Searching other resources

Web of Science Proceedings (the Institute for Science Information Proceedings allows access to abstracts from papers delivered at international conferences, symposia, seminars, colloquia, workshops and conventions); Health Management Information Consortium (HMIC focuses on community care and health systems management in the UK, Europe and developing countries including journals, books, reports, official publications and grey literature).

Bibliographies of included papers were assessed for relevant studies.

Experts were contacted for advice, and to identify additional published and unpublished references.

Industries were contacted for additional trials - Eli Lilly, Ferring, Novo Nordisk and Pharmacia.

Data collection and analysis

Selection of studies

Two independent researchers (JB and LB or CC) reviewed titles, abstracts and keywords of all records retrieved. Full articles were retrieved for further assessment if the information given suggested that the study was an RCT that: 1) included children with idiopathic short stature (ISS), 2) compared growth hormone (GH) with placebo or no treatment, 3) assessed one or more outcome measures. Full articles were also retrieved for clarification if there was some doubt about eligibility. Any disagreements were resolved through discussion with a third independent reviewer (RM).

Data extraction and management

The following data were extracted from each trial using a data extraction form:

- general information: authors, reference, country, year of publication, study design;
- intervention: dose, route, timing, control intervention (placebo or no treatment), any other treatment;

- participants: total number and number in comparison groups, age, sex, trial inclusion and exclusion criteria, height baseline characteristics, setting;
- outcomes specified above;
- results for outcomes listed as reported within trials;
- trial characteristics: methodological (allocation to treatment groups, blinding, baseline comparability, method of analysis and adequacy of sample size, and attrition), general (generalisability, appropriateness of outcome measures, intercentre variability, conflicts of interest);
- jadad quality assessment scale.

Data extraction was done by two reviewers (JB and LB or CC) with any disagreements resolved through discussion.

Assessment of risk of bias in included studies

Assessment of the quality of reporting of each trial was based on the quality criteria specified by Jadad (Jadad 1996). This scale assesses:
1) Minimisation of selection bias: was the study described as randomised, and was the method to generate randomisation described and appropriate.
2) Minimisation of detection bias: was the study described as double blind and was the method of blinding described and appropriate; were the outcome assessors blind to the intervention.
3) Minimisation of attrition bias: were withdrawals and dropouts described and quantified.
Based on these criteria, studies were broadly subdivided into the following three categories (see Cochrane Handbook):
A: All quality criteria met: low risk of bias.
B: One or more of the quality criteria only partly met: moderate risk of bias.
C: One or more quality criteria not met: high risk of bias.
Quality criteria were assessed by two researchers (JB and LB or CC), with any disagreements resolved through discussion.

Data synthesis

The clinical effects of human growth hormone in children was synthesised through a qualitative review with full tabulation of results of all included studies. Final height results were reported in centimetres and in SD relative to a normal adult population (as reported within trials). Short-term height results were reported as point estimates of growth velocity or as changes in growth velocity. Height outcomes were continuous data expressed as weighted mean differences (WMD) and an overall WMD was calculated. Where appropriate to combine results from multiple studies, meta-analyses were conducted. Because of highly underpowered tests of heterogeneity (P values), meta-analyses were calculated based on a random effects model. Calculations based on a fixed effects model did not differ substantially from the random effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was not performed due to insufficient data. Should sufficient data in future permit, the following subgroup analyses would be of interest.
- duration of treatment: Fewer than four years versus more than four years;
- injection frequency: Three times weekly versus six or seven times weekly;
- age at onset of growth hormone therapy;
- dose of growth hormone;
- gender.

Sensitivity analysis

There were insufficient data to allow any sensitivity analyses. Should sufficient data in future permit, the following sensitivity analyses would be of interest:
- repeating the analysis excluding any unpublished studies;
- repeating the analysis taking account of study quality, as specified above;
- repeating the analysis excluding any very large studies to establish how they dominate the results.

The analysis was carried out using MetaView 4.1 in Review Manager 4.2.8 (Cochrane software).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Searches identified 1202 records. Titles and abstracts and keywords of all records were reviewed by two reviewers (JB and LB or CC). Any disagreements were resolved through discussion. From this review 1182 references were excluded. The reasons for exclusion were: studies not conducted in humans, studies conducted in adults, studies in participants who did not have ISS, studies in which growth hormone (GH) was not administered, studies in which there was no untreated group, studies in which there was no control group, studies in which groups were not randomised or quasi randomised, studies in which there was no growth outcome, studies of human growth hormone dose (without a "zero dose" group) and reports of results from databases.
On the basis of review of the abstracts, 20 full records were retrieved. Abstracts had suggested that they would meet inclusion

criteria or there was a need for additional information to determine whether the study met inclusion criteria. These full reports were assessed by two researchers (JB and LB or CC) (reference citations are included for all retrieved references, either as included or excluded studies). Based on review of the full reports eight studies were excluded. These are listed in Characteristics of excluded studies with reasons for exclusion.

Ten studies met the inclusion criteria, reported in twelve papers (Kamp 2002 reporting quality of life data as Theunissen 2002, and Leschek 2004 reporting psychological adaptation as Ross 2004). Seven were sponsored by or received support from pharmaceutical companies. Four studies were conducted in the UK, one each in USA, Italy, Egypt, The Netherlands, Australia/New Zealand and USA/Chile.

Included studies

Studies and participants

All ten studies were randomised controlled trials. The studies included between 18 and 121 participants and only four studies (Genentech 1989; Ackland 1990; Cowell 1990;Leschek 2004) comprised more than 50 participants. Inclusion criteria for participants were broadly similar, specifying short normal children less than the 3rd percentile in height, with no chronic illness or dysmorphic syndromes. Six studies (Genentech 1989; Ackland 1990; McCaughey 1994; Barton 1995; Soliman 1996; Kamp 2002) included children who were prepubertal, one peripubertal (Leschek 2004) and two (Volta 1993; McCaughey 1998) had pubertal children, one of which included girls only (McCaughey 1998).

Interventions

Seven of the trials (Genentech 1989; Volta 1993; McCaughey 1994; Barton 1995; Soliman 1996; Kamp 2002) compared GH-treated children with untreated controls, with an additional treatment group receiving luteinising hormone-releasing hormone analogue to delay puberty in one trial (Volta 1993) and an additional group of participants who did not give consent to randomisation in another trial (McCaughey 1998). Three studies (Cowell 1990; Ackland 1990; Leschek 2004) were placebo controlled, with an additional observation group in one (Ackland 1990). Two of the three earlier trials used doses of 0.3 mg/kg/wk (Genentech 1989; Ackland 1990), one used either 0.2 or 0.4 mg/kg/week (Cowell 1990) and one 0.22 mg/kg/week (Leschek 2004). The studies which commenced later computed dosages based on body surface area. Doses ranged from low doses of 5 mg/m^2/week (Soliman 1996) and 5.33 mg/m^2/week (Volta 1993) to higher doses of 6.67 or 13.33 mg/m^2/week (Barton 1995), 10 mg/m^2/week (McCaughey 1998; McCaughey 1994). In the study with the highest dose of 14 mg/m^2/week children received GH treatment for two periods of three months (either 3.5 mg/m^2/week or 7.0 mg/m^2/week) separated by two three month washout periods during the first year before starting high dose GH treatment in the second year of study (Kamp 2002).

Outcomes

Only one study had a follow-up time long enough to report near final height (McCaughey 1998). One study reported adult height as adult height SDS (Leschek 2004). All the other studies were short-term and reported short-term outcomes such as growth velocity or height standard deviation score at baseline to six months (Cowell 1990; Ackland 1990), or baseline to one year (Soliman 1996; Genentech 1989; Barton 1995; Volta 1993) or three years (McCaughey 1994). One study reports results after two years of growth hormone treatment (Kamp 2002). This study also reported health related quality of life in children treated for ISS, using three different instruments. The TNO/AZL (TACQOL) Children Quality of life questionnaire which is a 56-item instrument used in medical research and clinical trials; ISSQOL questionnaire, an 8-item ISS-specific scale covering vitality; Dutch children's quality of life questionnaire (DUCATQOL) which is a 25-item generic self-report instrument for school-aged children with reported good validity and reliability. The study which reported adult height SDS also reported psychological adaptation using the Self-Perception Profile (SPP) and Silhouette Apperception test (SAT), with a Child Behaviour Checklist (CBCL) completed by the primary care-taking parent (Leschek 2004). Adverse effects were reported in five studies (Genentech 1989; McCaughey 1994; Barton 1995; McCaughey 1998; Leschek 2004). No study presented any cost data.

Risk of bias in included studies

The methodological quality of the included studies was assessed using the Jadad scale.

None of the included studies was of good quality. Only two of the trials were of moderate quality, although neither described the randomisation method used, and one did not give details of withdrawals (Ackland 1990) and the other did not give details of blinding (Leschek 2004). All of the six trials of poor quality (Cowell 1990; McCaughey 1994; Barton 1995; Soliman 1996; McCaughey 1998; Kamp 2002) did not describe the method of randomisation used, five lacked any mention of blinding (McCaughey 1994; Barton 1995; Soliman 1996; McCaughey 1998; Kamp 2002) and one did not give details of blinding or withdrawals (Cowell 1990). The trials of very poor quality (Genentech 1989; Volta 1993) did not give adequate description of randomisation, did not mention blinding, and dropouts and withdrawals were not clearly described.

Effects of interventions

(for details see Appendix 2 to Appendix 6)

Near final height

Only one randomised controlled trial reported near final height (McCaughey 1998). This study reported that near final height was significantly greater after growth hormone (GH) treatment in a study of pubertal girls in which the GH group was 7.5 cm and 6 cm taller than the two control groups (untreated controls and the group that did not give consent to randomisation), respectively (GH group, 155.3 cm ± 6.4; control, 147.8 cm ± 2.6; non-consent, 149.3 cm ± 3.3; P = 0.003, growth hormone versus control and non-consent groups).

Near final height standard deviation score (HtSDS) was significantly greater after GH treatment. Near final HtSDS for GH-treated girls was -1.14 ± 1.06 compared with -2.37 ± 0.46 in the control group and -2.13 ± 0.55 in the group not consenting to randomisation (P = 0.004 for GH group versus control and non-consent groups) (McCaughey 1998).

Adult height SDS

One RCT reported adult height standard deviation scores (HtSDS) (Leschek 2004). At study termination adult height was greater in the GH treated group (-1.77 ± 0.17 SDS, least squares mean ± SEM) than in the placebo group (-2.34 ± 0.17 SDS) by 0.57 SDS (3.7 cm; 95% confidence interval 0.03 to 1.10; P < 0.04).

Short term growth outcomes

Height standard deviation score (HtSDS)

Five studies reported HtSDS. In one trial (Soliman 1996), a change in HtSDS was shown after one year of GH treatment in prepubertal children, where HtSDS changed from -2.55 ± 0.5 to -1.7 ± 0.45 in the GH group, compared with a change from -2.8 ± 0.96 to -2.6 ± 0.9 in untreated controls (P < 0.05) (weighted mean difference 0.90; 95%confidence interval 0.33 to 1.47). In another trial (Volta 1993), a significant change in HtSDS from baseline was reported after one year of GH treatment in pubertal children in whom HtSDS changed from -2.2 ± 0.2 to -1.7 ± 0.2 (P <0.05), compared with no change in untreated controls (weighted mean difference 3.90; 95% confidence interval 3.46 to 4.34). Kamp 2002 showed no statistically significant differences between treated and untreated groups at one year. Another trial (Barton 1995) testing prepubertal children also found no statistically significant differences in HtSDS between treated and untreated children after one year, even when considering a high dose of GH (40 U/m^2/week). HtSDS significantly increased at two years from -2.9 ± 0.6 to -1.8 ± 0.5 in GH treated children compared to controls in whom HtSDS changed from -2.7 ± 0.3 to -2.6 ± 0.5 (P < 0.001) (Kamp 2002). In one trial, HtSDS in GH-treated prepubertal children with ISS changed from -2.4 to -1.2 at three years, compared with no change from -2.4 in untreated controls (P < 0.001) (McCaughey 1994).

Growth velocity (GV)

Five studies reported GV. Meta-analysis of the three trials reporting GV at one year showed a statistically significant greater GV in children treated with growth hormone compared with untreated controls (weighted mean difference 2.48; 95% confidence interval 2.06 to 2.90). The increase in GV from baseline to one year in prepubertal children (4.7 ± 1.2 to 7.3 ± 1.2 cm/yr, P < 0.00005) and pubertal children (4.3 ± 0.8 to 8.4 ± 0.9 cm/yr, P = 0.001) treated with GH was significantly greater than in untreated controls in one study (Genentech 1989). Another study (Soliman 1996) also reported GV significantly greater after one year GH treatment (4.2 ± 0.9 to 7.6 ± 1.2 cm/yr) compared with the control group (from 4.5 ± 1.6 to 5.5 ± 1.5; GH versus control, P < 0.05). One study (Volta 1993) reported GV after one year, with a significant increase in pubertal children treated with GH (from 4.4 ± 0.3 to 8.0 ± 1.0 cm/yr; P < 0.05), and untreated controls also showing a smaller but significant increase (from 4.7 ± 0.4 to 6.6 ± 0.6; P < 0.05), attributed by the authors of the study to the beginning of the pubertal growth spurt in some controls. In another study (McCaughey 1994), a significant difference in GV at three years was found between GH-treated prepubertal children and untreated controls: 6.4 cm/yr versus 5.2 cm/yr, respectively (P < 0.003). The one study which considered near final height in girls (McCaughey 1998), found no statistically significant difference in GV between treated and untreated groups, P = 0.21. In the fifth study reporting GV (Cowell 1990), GV was significantly increased after only six months treatment compared with placebo (no P value reported).

Growth velocity standard deviation score (GVSDS)

GVSDS showed a significant increase in GH-treated children at one year in prepubertal children, (P < 0.001) (Barton 1995) and pubertal children (P < 0.05) (Volta 1993) compared with untreated controls, and at six months in prepubertal children compared with those receiving placebo (P < 0.0001) (Ackland 1990).

Quality of life

Only one study reported health related quality of life (Theunissen 2002) in which children with ISS completed questionnaires three times in two years. At the start, children with ISS did not have lower scores than the norm population, except for social functioning. Children in the GH-treated group reported no improvement

in health related quality of life, or sometimes even worse, health related quality of life than the control group.

Psychological adaptation

Short stature among children with ISS was not associated with problems in psychological adaptation or self-concept with the psychological instruments employed in the study which reports the effects of GH treatment until adult height is attained (Leschek 2004, Ross 2004). GH treatment was associated with a trend toward improvement in problem behaviour as measured by questionnaires completed by parents of study participants.

Adverse effects

No serious adverse effects were reported in the included studies. One trial reported that children in the GH-treated group were relatively hyperinsulinaemic, with their mean fasting insulin levels significantly greater than those in the untreated group: 66.7 ± 13.8 versus 44.5 ± 7.2 insulin pmol/L, respectively, ($P < 0.01$) (McCaughey 1994).

DISCUSSION

Results from the published randomised controlled trials suggest that growth hormone (GH) therapy is effective in promoting growth in children with idiopathic short stature (ISS) in the short term, and significant changes can be achieved when assessed using height standard deviation scores and growth velocity measures. Studies suggest that short-term height gains can range from none to approximately 0.7 SD over one year. The study that reports adult height SDS suggests a height gain of 0.57 SDS in children treated with GH compared with those given a placebo, which equates to about 3.7 cm. Results from the one RCT reporting near final height found that treated girls were approximately 7.5 cm taller than girls randomised to the control group and 6 cm taller than girls who refused consent. However, these increases are such that treated individuals remain relatively short when compared with peers of normal stature, with heights near the lower bound of the normal range (i.e. approximately 2 SD below the normal mean). Growth and final height are dependent, not only upon hormonal factors, but also on the genetic endowment from parents, which should be considered when establishing realistic expectations about the potential effects of GH on final height. Also, it has been shown that growth hormone treatment can result in a high rate of bone maturation and an earlier onset of puberty with the paradoxical effect of shortening the growth period and premature closure of the epiphyses which may not be followed by a gain in final height (Kamp 2002).

It has been considered that final height is the best indicator of the effectiveness of GH in promoting growth given the natural variations in growth velocity. However, the available evidence on final height is extremely limited. Only one study that used the best methodology of double-blind placebo control has been conducted to final height but reported outcomes as adult height SDS rather than final height. Therefore, conclusions about the effects of GH on final height are tenuous. Another concern relating to the literature is that the children who are considered in the studies of ISS are quite heterogenous, and therefore generalisations are difficult. Additionally, outcomes other than height are not well represented in the literature. Only one of the studies included in the review considered quality of life issues, and could provide no evidence to support the commonly held assumption that growth hormone treatment improves health related quality of life in children with ISS. Another study concluded that short stature in children with ISS is not associated with problems in psychological adaptation or self-concept.

Another important consideration is whether shortness is an impediment to a healthy childhood. It is important to bear in mind that, although it may be of considerable value to increase the height of children who may be dramatically shorter than their peers, there will always be children who make up the lowest percentiles on the height distribution curve.

The issue of treatment compliance should also be noted. GH treatment generally requires taking injections six to seven times per week for several years. If the treatment regimen is not adhered to closely, effectiveness could be compromised. Compliance is also important because it will have an impact on costs and cost-effects. A recent review (Bryant 2002) estimated the incremental cost of GH treatment for one child with ISS to be between £50,000 and £70,000 (34,800 to 48,720 Euros), and the annual cost of GH treatment of a 30-kg child to be between £8,000 and £11,800 (5,570 to 8,210 Euros). The incremental cost of each centimetre in final height gained due to GH treatment was estimated to be between £13,500 and £27,200 (9,400 to 18,930 Euros), but could range from £4,295 to £272,020 (2,990 to 189,325 Euros). Another study (Lee 2006) has estimated the incremental cost-effectiveness ratio of GH therapy compared with no therapy for ISS in prepubertal boys as over $US52,000 (over 40,600 Euros). These issues are of particular importance in ISS and the use of an intervention for children who are not ill.

Very few adverse events were reported in the included studies. However, only a relatively small number of children participated in these studies, and potentially important adverse effects may not be detected in the context of such small trials. Over longer term surveillance and outside the context of randomised controlled trials it seems that adverse effects are rare, but can be serious, such as diabetes mellitus, slipped capital femoral epiphyses and malignancies (GH Soc 2001). Care should be taken in monitoring for adverse effects, and reporting them in randomised controlled trials.

AUTHORS' CONCLUSIONS

Implications for practice

The reported results suggest that growth hormone does improve growth and final height in idiopathic short stature. Although treated individuals may be taller than non-treated individuals, they are still relatively short compared with peers of normal height. Therefore whether the small expected gain in height is substantial enough to merit frequent or daily injections for a number of years in children who do not have a disease is not clear. Additionally, there is no evidence that growth hormone treatment improves health related quality of life or psychological adaptation. The cost of growth hormone is also substantial and it is a matter of debate as to whether the gains in height justify the expense. If large numbers of children with idiopathic short stature were to seek growth hormone treatment, this would have significant cost implications. Finally, although serious adverse effects may be rare, their possibility must also be taken into consideration.

Implications for research

Randomised controlled trials are required that focus on clear outcomes such as final height, rather than outcomes which are poorly predictive surrogate markers (such as predicted adult height or target height). In addition to growth hormone effects on height, research should address adverse effects, quality of life and psychosocial outcomes in children who are treated and focus particularly on measures that can be used in economic modelling. These trials should be analysed on an intent-to-treat basis. Other outstanding issues to be addressed in future research include age of onset of treatment, optimal dose of treatment, psychological issues, and heterogeneity of participants in studies (which could be masking a subset of those who could benefit long term).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ackland 1990

Methods	RCT (UK) Allocation to treatment groups: randomised, method not reported Blinding: double blind RCT (patients and health workers). Not clear if those assessing outcomes were blinded Comparability of treatment groups: groups comparable at baseline on age, height SDS and height velocity SDS (data not presented) Method of data analysis: number of patients included in the analysis was 89, therefore does not appear to be ITT analysis. Point estimates and confidence intervals/standard deviations were not reported. Statistical analysis used Pearson product-moment correlation coefficients and t-tests (paired and unpaired) for within and between group comparison. Repeat profiles assessed using Wilcoxon signed rank test Sample size / power calculations: no power calculations. Attrition / drop-out: not reported. Results described for 89 patients
Participants	Total: 95 children (77% male). Numbers per treatment group were not reported Characteristics of target population: Short children; height less than/ equal to 3rd centile (Tanner & Whitehouse); >5 years; pre-pubertal; normal birth weight for GA; GH response to pharmacological testing >15 mU/l Participants: mean age 9.7 years (range 5 to 14.2 years); mean Ht SDS - 2.7 (range -4.2 to -1.6); mean GV SDS over previous year -1.2 (range -3.0 to +1.1) Exclusion criteria: chronic disease / dysmorphic syndromes; Turners syndrome Setting: not specified.
Interventions	Treatment arms: Group A: placebo by injection, 3 times per week. Group B: GH 0.27 IU/kg (0.1 mg/kg) 3 times per week by sc injection. (Humatrope). Group C: observation. Length of treatment: 6 months. Other interventions used: none reported
Outcomes	GV SDS
Notes	Generalisability: inclusion and exclusion criteria were clearly defined Outcome measures: RCT was short term (6 months). Final height was not reported. Focused on GH secretion Inter-centre variability: number of centres taking part was not reported Conflict of interests: funding support from Eli Lilly and Adint Trust

Barton 1995

Methods	RCT (UK) Allocation to treatment groups: randomised, method not reported Blinding: echocardiographer was blinded. Otherwise no blinding was reported Comparability of treatment groups: groups reported to be similar in growth and endocrine parameters. Appears to be difference in sex ratio between groups Method of data analysis: ITT analysis for one year data. Point estimates and confidence intervals of differences between groups were not reported. Non-parametric analysis of variance used (Kruskal-Wallis) and Mann-Whitney. Changes within groups over time analysed by Wilcoxon matched pairs signed rank sum test. Sample size / power calculations: small sample size may have lacked power to detect significant differences between groups. No power calculation. Attrition / drop-out: none in year one.
Participants	Total number: 29 children (83% male) Observation: 9 children (89% male) Std GH: 10 children (60% male) High GH: 10 children (100% male) Characteristics of target population: Short pre-pubertal normally growing, children attending growth clinics; HtSDS < -1.5 for age and sex; GVSDS > -1.5 over preceding 12 months (Tanner & Whitehouse) Participants median(range): age 7.3 to 7.9 (5.1 to 9.5 years); BA delay 0.0 to 0.6 (-1.8 to 2.3); SDS -2.0 to -2.2 (-3.1 to -1.1); GVSDS -0.59 to -0.25 (-1.68 to 0.89); peak GH mU/l 12.6 to 15.6 (1.5 to 47.7) Exclusion criteria: history of significant cardiovascular, respiratory or renal disease Setting: 2 tertiary referral centres
Interventions	Treatment arms: 1. Observation 2. Std GH 20 IU/m2/wk by daily injection (Genotropin) 3. High GH 40 IU/m2/wk by daily sc injection (Genotropin) Length of treatment: 1 year Other interventions used: none reported
Outcomes	GV HtSDS/BA
Notes	Generalisability: inclusion and exclusion criteria were defined Outcome measures: short term study, final height was not reported. Inter-centre variability: 2 centres were involved but inter-centre variability was not assessed. Conflict of interests: funding support from Children Nationwide and Pharmacia, Stockholm

Cowell 1990

Methods	RCT (Australia/ New Zealand) Allocation to treatment groups: randomised, method not reported. Stratification for patient numbers at each of 8 centres Blinding: described as double blind. Treatment coded, so probably patients, health workers and study personnel were all blinded Comparability of treatment groups: no differences between randomised groups for pre-treatment variables Method of data analysis: analysis not on an ITT basis. Point estimates and CI of differences between treatment groups were not reported. Limited reporting of results. Wide age range may have included children undergoing puberty - no comment on influence of puberty on results Sample size / power calculations: no power calculation. Attrition / drop-out: not reported by treatment group. Reasons not given. 2 children did not complete study
Participants	Total number: 104 children (83% male) Placebo: 27 children GH (low dose): 37 children GH (high dose): 40 children Characteristics of target population: Short, slow growing children; normal provocative GH secretion (peak GH > 20 mU/l). 18% premature at birth Participants: mean CA 9.7 years (range 3.2 to 15.5 years); BA < 10 years in girls and < 12 years in boys; mean HtSDS -3 (range -5.0 to -1.91); mean GV 4.19 cm/yr (range 2.24 to 8.63 cm/yr); mean GVSDS -2.41 (range -4.72 to -0.16) Exclusion criteria: recognisable dysmorphic / skeletal disorders Setting: paediatric growth centres.
Interventions	Treatment arms: 1. Placebo 2. GH 0.6 IU/kg/wk (Genotropin) 3. GH 1.2 IU/kg/wk (Genotropin) Length of treatment: 12 months Other interventions used: none reported
Outcomes	GV
Notes	Generalisability: inclusion and exclusion criteria were defined Outcome measures: short term study. Final height not reported Inter-centre variability: not assessed. 8 different centres were involved Conflict of interests: funding support from Kabi Peptide Hormones, Stockholm

Genentech 1989

Methods	RCT (USA) Allocation to treatment groups: randomised, method not reported Blinding: assessor of bone age was blinded. Otherwise no blinding was reported Comparability of treatment groups: comparable at baseline (data presented) Method of data analysis: not ITT. Mean and SD. Student's t test for comparison with baseline and between groups. Pearson correlation for pairs of variable. Point estimates and confidence intervals of differences between treatment groups were not reported. Only pre-pubertal patients were included in the main analysis. No reasons given for exclusion of 4 patients in the control group from the analysis. Predicted adult height (Bayley and Pinneau, Roche, Tanner) Sample size / power calculations: no power calculation. Attrition / drop-out: not reported.
Participants	Total: 121 children (74% boys) GH: 63 children (73% male) Controls: 58 children (74% male) Characteristics of target population: Idiopathic short stature; Age =5 years or more; height 2SD or more below mean (< 3rd centile); birth weight = 2.5 kg or more; serum GH = 10 ng/ml or more on at least 1 test; BA girls = 9 years or less, boys BA = 10 years or less; pre-pubertal Participants: mean age 9.5 and 9.4 years; mean height SDS -2.8 (SD 0.5); BA 7.7 and 7.9 years; height velocity 4.4 (SD 2.1) cm/year; mean parental < mean for normal population, predicted adult height significantly less than normal adult height Exclusion criteria: diabetes mellitus; hypothyroidism; chronic systemic illness; malignancy; bone/cartilage dysplasia; psychosocial dwarfism; previous history GH treatment; treatment for hyperactivity. Subsequently, children who had progressed into puberty (plus 4 others) were excluded from the analysis Setting: not specified
Interventions	Treatment arms: 1. GH 0.1 mg/kg by injection, three times a week (Genentech) 2. No treatment Length of treatment: 1 year Other interventions used: not stated.
Outcomes	GV SDS scores for predicted adult height
Notes	Generalisability: inclusion and exclusion criteria were defined Outcome measures: final height not assessed. Short term study for GH v control (1 year). Inter-centre variability: not assessed. Study conducted at 10 sites Conflict of interests: study conducted by Genentech, California

Kamp 2002

Methods	RCT (Netherlands) Allocation to treatment groups: randomised, method not reported. Blinding: no blinding reported Comparability of treatment groups: comparable at baseline (data presented). Method of data analysis: not ITT. Baseline characteristics compared using unpaired t test. Auxological characteristics analysed using mixed model analysis of variance. Cumulative proportion of children in puberty tested using log rank test. Correction for confounding effects of age and sex using Cox regression model Sample size / power calculations: no power calculations. Attrition / drop out: drop outs described with reasons and by treatment allocation group. GH treated group drop out rate 15% (3/20) vs untreated control group rate 10% (2/20)
Participants	Total: 40 children GH treated: 20 children (65% male). 17 analysed Controls: 20 children (65% male). 18 analysed Characteristics of target population: Prepubertal, short normal children. Age 4-8 years for girls, 4-10 years for boys; height less than -2.0 SDS; normal body proportions; peak stimulated GH concentration greater than 10µg/l after provocation Participants: Mean age: 8.4 years (SD 1.7) GH treated group, 7.4 (SD 1.8) control group at entry. GH peak concentration on provocation µg/l: 27.9 (SD 22) GH treated group, 25.2 (SD 13) control group. Mean birth weight: GH Treated group 3.3 kg, control group 3.1 kg. Height SDS: GH treated group -2.9 (SD 0.6), control group -2.7 (SD 0.3) Exclusion criteria: evidence of malnutrition, hormonal, or systemic disease Setting: 3 participating hospitals
Interventions	Treatment arms: 1. GH 1.5 or 3.0 IU/m2/day for two periods of three months separated by two three month washout periods, then 6.0 IU/m2/day, by daily injections. (Genotropin) 2. Untreated control Length of treatment: at least two years. When puberty occurred GH treatment stopped at end of a complete year's treatment (eg three or four years treatment) Other intervention used: none reported.
Outcomes	HtSDS
Notes	Generalisability: inclusion and exclusion criteria defined. Outcome measures: HtSDS appropriate. Inter-centre variability: not assessed. 3 centres. Conflict of interests: funding from Pharmacia & Upjohn AB

Leschek 2004

Methods	RCT (USA/Chile) Allocation to treatment groups: randomised , stratified by gender and Bayley-Pinneau predicted height Blinding: described as double blind, details not given. Comparability of treatment groups: no differences between treatment groups in treatment duration, chronological age or bone age. Method of data analysis: not ITT. ANCOVA of adult height SDS. Adverse event frequency analysed by Fischer's exact test Sample size / power calculation: planned sample size was 80 subjects which provided 80% power to detect a 3cm difference in mean adult height between the two treatment groups Attrition / drop-out: drop-outs described with reasons and by treatment group. GH group 40% (15/37), placebo group 65% (20/31) for adult height measurement
Participants	Total: 68 children GH treated: 37 children (78% male). Placebo group: 31 children (77% males). Characteristics of target population: Age 10-16 (boys) or 9-15 (girls), bone age =< 13 yr (boys) or =< 11 yr (girls), marked proportionate short stature (SDS =<-2.5), peripubertal, peak stimulated GH more than 7μg/l Participants: Mean age: 12.5 years (SD 1.6) GH treated group, 12.9 (SD 1.1) placebo group. Bone age: 11.1 years (SD 1.5) GH treated group, 11.7 (SD 1.1) placebo group. Height SDS: -2.7 (SD 0.6) GH treated group, -2.8 (SD 0.6) placebo group Exclusion criteria: chronic illness, known genetic syndrome, ever received GH, oestrogen or androgen treatment, or currently receiving any drug likely to affect growth Setting: not specified
Interventions	Treatment arms: 1. GH 0.22 mg/kg/week divided into three doses per week (Humatrope) 2. Placebo sc Length of treatment: mean treatment duration 4.4 years. Other intervention used: not stated.
Outcomes	Adult height SDS
Notes	Generalisibility: Inclusion and exclusion criteria defined. Outcome measures: Adult height SDS appropriate. Inter-centre variability: not assessed. Conflicts of interest: funded in part by Eli Lilly and Co.

McCaughey 1994

Methods	RCT (UK) Allocation to treatment groups: randomised, method not reported Blinding: assessor of bone age was blinded. No mention made of blinding of other outcomes assessed Comparability of treatment groups: reported as similar at baseline on age, sex, height, parental height, birth details, bone age delay, socio-economic status and evidence of psychosocial deprivation (no supporting data) Method of data analysis: analysis not reported as being on ITT basis. Point estimates and CI of difference between groups were not reported. Used t-tests and Mann Whitney tests to compare groups Sample size / power calculations: no power calculations. Small sample size may lack power to detect significant differences Attrition / drop-out: drop outs described with reasons and by treatment allocation group. GH treated group drop-out rate 29% (6/21) v untreated control group rate 30% (6/20)
Participants	Total: 41 children GH treated: 21 children (52% male) Controls: 20 children (60% male) Characteristics of target population: Prepubertal, short normal children of similar age and social class; height more than 2 SD below mean (Tanner and Whitehouse); with adequate stimulated growth hormone Participants: Mean age: 7.8 years (SD 0.5) at entry. GH concentration: >7.5 µg/l (15 mU/l) to either clonidine or sleep. Mean birth weight: GH Treated 2800g, controls 2813 g. Exclusion criteria: known pathology and recognisable causes of short stature excluded by clinical examination and screening tests (not specified). Low birth weight was not an exclusion criteria. No details were given of method used to select sample, which had narrow age band (small SD). Setting: selected from community (no details)
Interventions	Treatment arms: 1. GH 30 IU/m2/wk by daily injections (autoinjector) (Genotropin) 2. Untreated control Length of treatment: 3 years Other interventions used: none reported.
Outcomes	HtSDS GV GVSDS Final /near final height (not defined) Predicted final height
Notes	Generalisability: inclusion and exclusion criteria were defined Outcome measures: Final / near final height was not defined so not clear if the use of this measure is appropriate Inter-centre variability: number of centres not specified. Authors from one site Conflict of interests: funding support from Kabi Pharmacia UK Ltd and AB Sweden

McCaughey 1998

Methods	RCT (UK) Allocation to treatment groups: randomised, method not reported Blinding: none Comparability of treatment groups: no significant difference between groups regarding mean pattern of growth; height; height SDS; proportion with familial short stature. Significant different at baseline regarding difference between bone age and chronological age, mean target height. Higher GV in non-consenting controls compared to other groups Method of data analysis: not ITT. Point estimates and confidence intervals of differences between groups was not given. Data analysed with SPSS. Means of paired data compared with Student's t test, unpaired data with Student's t test or one-way ANOVA. Mann Whitney U or Kruskal-Wallis tests as appropriate for small numbers Sample size / power calculations: very small sample size with no prior power calculation Attrition / drop-out: drop outs described with reasons and by treatment allocation group. GH group 30%, untreated control 25%, non-consent control 14%
Participants	Total number: 40 girls GH treatment: 10 girls Randomised control: 8 girls Non-consent control: 22 girls Characteristics of target population: Normal girls of height >=2 SD below mean height for age. Participants: Mean age at start of treatment 8.07±0.48 years. All had reached at least stage 4 breast development and menarche before stopped treatment Exclusion criteria: children with disorders (refs given but no details in report), coeliac disease. References given to tests used to exclude pathology but no details in text Setting: selected from community screening at school entry (Wessex Growth study)
Interventions	Treatment arms: 1. GH 30 IU/m2/wk daily injections (Genotropin) 2. Randomised untreated controls 3. Non-randomised untreated controls Mean length of treatment: 6.2 years Other interventions used: none reported.
Outcomes	Near-final height data: Height. HtSDS. GV. Near-final height minus target height. Near-final height minus predicted height.
Notes	Generalisability: inclusion / exclusion criteria were defined Outcome measures: Appropriate outcome measures used. Tanner Whitehouse data used for childrens' standards Inter-centre variability: appears to be only 1 centre involved Conflict of interests: support from Pharmacia and Upjohn Ltd

Ross 2004

Methods	RCT (USA/Chile) Allocation to treatment groups: randomised , stratified by gender and Bayley-Pinneau predicted height Blinding: described as double blind, details not given. Comparability of treatment groups: no differences between treatment groups in treatment duration, chronological age or bone age. Method of data analysis: mean ± SD on year by year scores for CBCL. Change from baseline for CBCL scores by t test. Wilcoxon signed rank tests for SAT change from baseline scores at year 1-4. Wilcoxon rank sum tests to compare GH and placebo groups for year by year SAT scores. No point estimates with confidence intervals given for SAT and SPP Sample size / power calculation: no power calculation for psychological outcomes Attrition / drop-out: drop-outs described with reasons and by treatment group. GH group 76% (28/37), placebo group 90% (28/31)
Participants	Total: 68 children GH treated: 37 children (78% male). Placebo group: 31 children (77% males). Characteristics of target population: Age 10-16 (boys) or 9-15 (girls), bone age =< 13 yr (boys) or =< 11 yr (girls), marked proportionate short stature (SDS =<-2.5), peripubertal, peak stimulated GH more than 7μg/l Participants: Mean age: 12.5 years (SD 1.6) GH treated group, 12.9 (SD 1.1) placebo group. Bone age: 11.1 years (SD 1.5) GH treated group, 11.7 (SD 1.1) placebo group. Height SDS: -2.7 (SD 0.6) GH treated group, -2.8 (SD 0.6) placebo group Exclusion criteria: chronic illness, known genetic syndrome, ever received GH, oestrogen or androgen treatment, or currently receiving any drug likely to affect growth Setting: not specified
Interventions	Treatment arms: 1. GH 0.22 mg/kg/week divided into three doses per week (Humatrope) 2. Placebo sc Length of treatment: mean treatment duration 4.4 years. Other intervention used: not stated.
Outcomes	CBCL, SPP and SAT
Notes	Generalisibility: Inclusion and exclusion criteria defined. Outcome measures: SAT and SPP appropriate. CBCL completed by parent Inter-centre variability: not assessed. Conflicts of interest: funded in part by Eli Lilly and Co.

Soliman 1996

Methods	RCT (Egypt) Allocation to treatment groups: randomised, method not stated, after determination of GH status Blinding: not stated. Comparability of treatment groups: No differences in baseline GV and HtSDS of patients and controls (no other baseline comparisons) Method of data analysis: not ITT analysis. not ITT analysis. Data presented as mean±SD. Paired Student t-test used to analyse changes in each group before treatment and after 1 year. Simple linear regression was used to test correlation between variables. No point estimates with confidence intervals given Sample size/power calculation: Not stated. Attrition/drop-out: no withdrawals or dropouts in group III.
Participants	Total number: 77 children (sex not stated). IIIa GH 15 U/m2/wk: 12 patients. IIIb control: 12 patients. (Ia, Ib, IIa and IIb: 53 patients, growth hormone deficient, not reported here) Characteristics of target population: <3rd percentile in height; prepubertal; peak GH response to clonidine and insulin provocation was >10 mg/l in group III Participants Group III (mean ± sd): age 7±1.5; GV 4.5±1.6; HtSDS 2.8±0.96. Bone age <10 years. Exclusion criteria: reduced weight to height; systemic disease; history of head trauma or cranial irradiation; malnutrition; psychosocial dwarfism or hypothyroidism Setting: Outpatient clinic.
Interventions	Treatment arms. IIIa 15 U/m2/wk IIIb untreated control. (Ia, Ib, IIa, IIb not reported here) Length of treatment: 1 year. Other interventions used: not stated.
Outcomes	Height GV HtSDS.
Notes	Generalisability: Inclusion and exclusion criteria defined. Outcome measures: Appropriate outcome measures used, but not final height. HtSDS calculated as (X1 - X2)/SD where X2 and SD are age matched population mean height and SD, and X1 is the subject height. Normal population data according to Tanner. Group III (n=24) part of larger trial with complicated design. Group IIIa and IIIb comprised non-GH deficient children, Group IIIa treated with GH, Group IIIb controls Conflict of interests: Not stated.

Theunissen 2002

Methods	RCT (Netherlands) Allocation to treatment groups: randomised, method not reported. Blinding: no blinding reported Comparability of treatment groups: comparable at baseline (data presented). Method of data analysis: not ITT. Baseline characteristics compared using unpaired t test. Between groups Mann-Whitney U test Sample size / power calculations: no power calculations. Attrition / drop out: drop outs described with reasons and by treatment allocation group. GH treated group drop out rate 10% (2/20) vs untreated control group rate 25% (5/20) for psychiatric assessment
Participants	Total: 40 children GH treated: 20 children (75% males). 18 analysed Controls: 20 children (70% male). 15 analysed Characteristics of target population: Prepubertal, short normal children. Age 4-10; height less than -2.0 SDS; normal body proportions; no GH deficiency; no evidence of chronic organic disease; no psychiatric disease Participants: Age 5-7: 9 (45%) GH treated group, 11 (55%) control group. Age 8-12: 11 (55%) GH treated group, 9 (45%) control group. Exclusion criteria: evidence of malnutrition, hormonal, or systemic disease Setting: 3 participating hospitals
Interventions	Treatment arms: 1. GH 1.5 or 3.0 IU/m2/day for two periods of three months separated by two three month washout periods, then 6.0 IU/m2/day, by daily injections. (Genotropin) 2. Untreated control Length of treatment: at least two years. When puberty occurred GH treatment stopped at end of a complete year's treatment (eg three or four years treatment) Other intervention used: none reported.
Outcomes	HRQoL questionnaires: (TNO-AZL Children's Quality of Life (TACQOL) Questionnaire); Idiopathic Short Stature Quality of Life (ISSQOL) Questionnaire; Dutch Children's AZL/TNO Quality of Life (DUCATQOL) Questionnaire
Notes	Generalisability: inclusion and exclusion criteria defined. Outcome measures: HRQOL measures may not be validated. Inter-centre variability: not assessed. 3 centres. Conflict of interests: funding from Pharmacia & Upjohn AB

Volta 1993

Methods	RCT (Italy) Allocation to treatment groups: randomised, method not reported Blinding: none Comparability of treatment groups: reports no differences present at baseline in auxological parameters (values presented in table). Sex distribution varies between groups Method of data analysis: results presented as mean ± SE for all 18 children entered so seems to be ITT. Differences between groups reported in terms of statistical significance and point estimate, no CI of differences given. Paired Students t-test used for intragroup evaluations, and ANOVA corrected by Bonferroni for multiple comparisons among independent groups. Height prognosis using Bayley and Pinneau method Sample size / power calculations: very small sample size, no prior power calculations Attrition / drop-out: no drop outs.
Participants	Total: 18 children (9 male, 9 female) Control: 6 children (3M, 3F) GH: 6 children (4 M, 2F) GH+LHRHa: 6 children (2M, 4F) Characteristics of target population: Pubertal children with familial short stature. Participants: Mean age 11.9±0.4 years (range 10.4 to 13.7); genetic target < 10th centile; height < 3rd centile; bone age within 2 SD for CA; height prognosis < 3rd centile; pubertal stage B 2-3 for girls and G2-3 for boys (Tanner); normal GV for CA; normal birth weight; plasma GH levels after pharmacological stimulation > 10 ng/ml; basal and LHRH stimulated LH and FSH consistent with first stage of puberty Exclusion criteria: dysmorphic syndromes, chronic disease. Good definition of characteristics of sample. Very small sample size limiting power to detect differences. Differing sex ratios among groups Setting: Growth Clinic, 2 centres.
Interventions	Treatment arms: 1. No treatment. 2. GH 16 U/m2/wk in 4 injections (Genotropin) 3. GH as above plus LHRHa (Suprefact) 1,200 µg/day intranasally Length of treatment: 1 year Other interventions used: none reported
Outcomes	HtSDS GV GVSDS related to bone age Height prognosis SDS
Notes	Generalisability: inclusion criteria broad. Outcome measures: appropriate outcomes, but no final height reported. Short term study over 1 year Inter-centre variability: Authors from 2 centres. No inter centre variability was assessed Conflict of interests: funding support not mentioned

CBCL Child Behaviour Checklist

HtSDS Height standard deviation score
GV growth velocity
GVSDS growth velocity standard deviation score
SAT Silhouette Apperception Test
SPP Self-Perception Test
Tanner -Whitehouse standard based on normal population

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Genentech 1990	Results reported in another study
Hopwood 1993	Results reported in another study
Ito 1993	Growth not primary outcome
Job 1994	No untreated group
Loche 1991	No untreated group
Phillip 1998	No untreated group
Rekers-Mombarg 1998	No untreated group
Wit 1995	Non-randomised controls

DATA AND ANALYSES

Comparison 1. Growth hormone vs no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final height (or near final height)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Growth velocity (1 year)	3	130	Mean Difference (IV, Random, 95% CI)	2.48 [2.06, 2.90]
3 Growth Velocity Standard Deviation Score (1 year)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Height Standard Deviation Score (2 years)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Adult Height Standard Deviation Score	1	33	Mean Difference (IV, Fixed, 95% CI)	0.57 [0.08, 1.06]

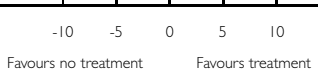
Analysis 1.1. Comparison 1 Growth hormone vs no treatment, Outcome 1 Final height (or near final height).

Review: Recombinant growth hormone for idiopathic short stature in children and adolescents

Comparison: 1 Growth hormone vs no treatment

Outcome: 1 Final height (or near final height)

Study or subgroup	Growth hormone N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
McCaughey 1998	10	155.3 (6.4)	8	147.8 (2.6)			7.50 [3.14, 11.86]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							



Analysis 1.2. Comparison 1 Growth hormone vs no treatment, Outcome 2 Growth velocity (1 year).

Review: Recombinant growth hormone for idiopathic short stature in children and adolescents

Comparison: 1 Growth hormone vs no treatment

Outcome: 2 Growth velocity (1 year)

Study or subgroup	Growth hormone N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Genentech 1989	50	7.3 (1.2)	44	4.7 (1.1)		81.7 %	2.60 [2.13, 3.07]
Soliman 1996	12	7.6 (1.2)	12	5.5 (1.5)		15.0 %	2.10 [1.01, 3.19]
Volta 1993	6	8 (2.45)	6	6.6 (1.47)		3.4 %	1.40 [-0.89, 3.69]
Total (95% CI)	**68**		**62**			**100.0 %**	**2.48 [2.06, 2.90]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.58$, df = 2 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 11.59 (P < 0.00001)

Analysis 1.3. Comparison 1 Growth hormone vs no treatment, Outcome 3 Growth Velocity Standard Deviation Score (1 year).

Review: Recombinant growth hormone for idiopathic short stature in children and adolescents

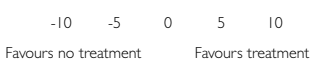
Comparison: 1 Growth hormone vs no treatment

Outcome: 3 Growth Velocity Standard Deviation Score (1 year)

Study or subgroup	GH Treatment N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Volta 1993	6	3.9 (3.18)	6	0.4 (2.45)			3.50 [0.29, 6.71]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



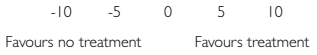
Analysis 1.4. Comparison 1 Growth hormone vs no treatment, Outcome 4 Height Standard Deviation Score (2 years).

Review: Recombinant growth hormone for idiopathic short stature in children and adolescents

Comparison: 1 Growth hormone vs no treatment

Outcome: 4 Height Standard Deviation Score (2 years)

Study or subgroup	GH Treatment N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kamp 2002	17	-1.8 (0.5)	18	-2.6 (0.5)			0.80 [0.47, 1.13]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							



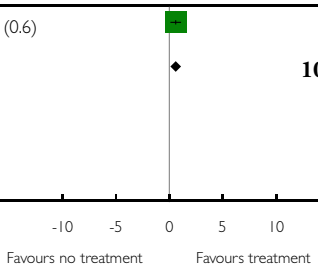
Analysis 1.5. Comparison 1 Growth hormone vs no treatment, Outcome 5 Adult Height Standard Deviation Score.

Review: Recombinant growth hormone for idiopathic short stature in children and adolescents

Comparison: 1 Growth hormone vs no treatment

Outcome: 5 Adult Height Standard Deviation Score

Study or subgroup	GH Treatment N	Mean(SD)	No Treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Leschek 2004	22	-1.77 (0.8)	11	-2.34 (0.6)		100.0 %	0.57 [0.08, 1.06]
Total (95% CI)	**22**		**11**			**100.0 %**	**0.57 [0.08, 1.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.29 (P = 0.022)							
Test for subgroup differences: Not applicable							



APPENDICES

Appendix 1. Search strategy

Search terms

Unless otherwise stated, search terms were free text terms; exp = exploded MeSH: Medical Subject Heading (Medline medical index term); the dollar sign ($) stands for any character(s); the question mark (?) = substitute for one or no characters; ab = abstract; ti = titel; tw = text word; ot = original titel; pt = publication type; sh = MeSH: Medical subject heading (MEDLINE medical index term) ; adj = adjacency.

I. Growth hormone:
1.exp growth hormone/ or exp human growth hormone/
2.exp Human Growth Hormone/
3.(somatropin$ or somatrophin$).tw.
4.(somatotropin or somatotrophin$).tw.
5.growth hormone$.tw.
6.(genotropin$ or humatrope$ or norditropin$ or saizen$ or zomacton$ or nutropin$).tw.
7.or/1-6

II. Short stature:
8.(short stature$ or small stature$).tw.

III. Short stature + growth hormone + children and adolescents:
9.7 and 8
10.limit 9 to "all child (0 to 18 years)"

IV. RCT/CCT (sensitive search)
Part 1:
11.randomized controlled trial.pt.
12.controlled clinical trial.pt.
13.randomized controlled trials.sh.
14.random allocation.sh.
15.double-blind method.sh.
16.single-blind method.sh.
17.or/11-16
Part 2:
18.clinical trial.pt.
19.exp clinical trials/
20.(clinic$ adj25 trial$).tw.
21.((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
22.placebos.sh.
23.placebo$.tw.
24.random$.tw.
25.research design.sh.
26.(latin adj square).tw.
27.or/18-26
Part 3:
28.comparative study.sh.
29.exp evaluation studies/

(*Continued*)

30.follow-up studies.sh.
31.prospective studies.sh.
32.(control$ or prospectiv$ or volunteer$).tw.
33.cross-over studies.sh.
34.or/28-33
35.17 or 27 or 34

V. III + IV:
36.10 and 35
37.limit 36 to animal
38.limit 36 to human
39.37 not 38
40.36 not 39

Appendix 2. TACQOL-CF (in SDS) (Theunissen et al, 2002)

Measure	Baseline GH treated	Baseline untreated	1year GH treated	1year untreated	2 year GH treated	2 year untreated	p time	p group	p time x group
Physical complaints	-1.11	-1.41	-1.50	-1.38	-1.67	-0.74**	0.74	0.30	0.05
Motor functioning	-0.10	-0.45	-0.14	0.43	-0.37	0.29**	0.74	0.17	0.24
Autonomy	-0.54	-0.69	-0.80	0.22	-0.41	0.13	0.59	0.14	0.16
Cognitive functioning	0.28	0.20	0.24	0.65	-0.11	0.44**	0.67	0.19	0.60
Social functioning	-2.37	-1.25	-1.68	-0.69	-2.64	-0.56***	0.22	0.00	0.61
Positive emotions	-0.51	-0.41	-0.78	-0.22	-0.75	0.10*	0.87	0.11	0.95
Negative emotions	0.05	0.00	-0.21	0.00	-0.17	0.03	0.14	0.66	0.80
Between group Mann	Higher scores represent bet-								

(*Continued*)

Whitney U test, *** p<0.01, ** p<0.05, * p<0.10	ter HRQOL								

Appendix 3. ISSQOL-CF (scale 0-100) (Theunissen et al, 2002)

Measure	Baseline GH treated	Baseline untreated	1 year GH treated	1 year untreated	2 year GH treated	2 year untreated	p time	p group	p time x group
Vitality	77	74	76	82	70	85*	0.59	0.13	0.04
Between groups MannWhitney U test, * p<0.01	Higher scores represent better HRQOL								

Appendix 4. DUCATQOL-CF (in SDS) (Theunissen et al, 2002)

Measure	Baseline GH treated	Baseline untreated	1 year GH treated	1 year untreated	2 year GH treated	2 year untreated	p time	p group	p time x group
Home	-0.15	-0.40	0.19	0.01	0.19	0.24	0.12	0.67	0.81
Physical	-0.12	-0.29	0.36	0.07	0.19	0.10	0.26	0.58	0.66
Emotional	0.10	-0.03	0.61	0.42	0.34	0.31	0.11	0.69	0.89
Social	-0.35	0.10	0.51	0.17	0.09	0.67	0.06	0.60	0.19

(*Continued*)

Total QOL (higher scores represent better HRQOL)	-0.16	-0.20	0.55	0.24	0.26	0.42	0.05	0.82	0.47

Appendix 5. Adverse effects

Study	GH treated group	Untreated group
Ackland 1990	none reported in publication	none reported in publication
Barton 1995	none reported in publication	none reported in publication
Cowell 1990	none observed	none observed
Genentech 1989	no adverse effects	no adverse effects
Kamp 2002	none reported in publication	none reported in publication
McCaughey 1994	acne (1/21)	asthma (1/20)
McCaughey 1998	Mean fasting insulin 66.7+/- 13.8 pmol/l	Mean fasting insulin 44.5 +/- 7.2 pmol/l (p<0.01)
Soliman 1996	none reported in publication	none reported in publication
Volta 1993	none reported in publication	none reported in publication
Leschek 2004	Mild/trace scoliosis 7/37; pubertal gynecomastia 2/37; mild hypergonadotropic hypogonadism 1/37. Some transient fasting plasma glucose effects reported	Mild/trace scoliosis 4/31; pubertal gynocomastia 1/31.

Appendix 6. CBCL change (mean ± SD, study year minus baseline) (Ross et al, 2004)

Measure	GH yr 1 (n=17)	GH yr 2 (n=23)	GH yr 3 (n=12)	GH yr 4 (n=9)	Placebo yr 1 (n=9)	Placebo yr 2 (n=19)	Placebo yr 3 (n=9)	Placebo yr 4 (n=3)
Social competences - activities	-3.2 ± 6.6	-3.6 ± 7.2	-2.2 ± 7.4	-4.6 ± 7.5	-2.8 ± 7.5	-3.5 ± 8.3	-5.8 ± 10.9	-4.7 ± 7.1

(*Continued*)

Social competencies - social	1.1 ± 7.8	0.3 ± 9.9	1.8 ± 11.6	6.5 ± 11.7	-4.5 ± 11.5	-3.1 ± 9.3	-1.7 ± 8.4	7.0 ± 6.6
Social competencies - school	-1.7 ± 5.5	-0.9 ± 6.3	0.9 ± 6.8	-2.6 ± 7.8	0.7 ± 3.8	0.4 ± 3.3	-0.7 ± 4.4	1.7 ± 2.9
Behaviour problems - Total	0.1 ± 6.5	-0.7 ± 6.9	-5.2 ± 8.8	-7.4 ± 9.5	1.4 ± 12.7	-3.8 ± 12.2	2.4 ± 9.0	8.7 ± 8.5
Behaviour problems - internalising	-1.8 ± 8.7	-2.5 ± 7.9	-5.4 ± 9.0	-5.3 ± 7.5	1.8 ± 12.2	-3.5 ± 11.5	1.7 ± 9.2	7.3 ± 12.1
Behaviour problems - externalising	0.5 ± 7.2	0.7 ± 6.3	-1.1 ± 6.5	-4.8 ± 7.8	1.9 ± 11.9	-0.6 ± 10.6	5.8 ± 8.0	9.3 ± 4.7
Social competencies positive scores indicates improvement; negative score indicates worsening. Behaviour problems positive score indicates worsening; negative score indicates improvement								

WHAT'S NEW

Last assessed as up-to-date: 30 December 2005.

Date	Event	Description
5 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 4, 2003

Date	Event	Description
31 December 2005	New search has been performed	This is an update of the first version of this review, published in issue 4, 2003

CONTRIBUTIONS OF AUTHORS

JACKIE BRYANT: selection of studies, quality assessment of trials, data extraction, drafting of protocol / review, data analysis, data presentation.

LOUISE BAXTER: selection of studies, quality assessment of trials, data extraction, drafting of update review, data analysis, data presentation

CAROLYN CAVE: searching for trials, selection of studies, data extraction, drafting of protocol / review, data analysis, data presentation.

RUAIRIDH MILNE: selection of studies, data extraction, drafting of protocol / review, data analysis, data presentation.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Wessex Institute for Health Research and Development, University of Southampton, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Body Height [*drug effects]; Growth Disorders [*drug therapy]; Growth Hormone [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]; Treatment Outcome

MeSH check words

Child; Female; Humans; Male