Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation

A Takeda, K Cooper, A Bird, L Baxter,
GK Frampton, E Gospodarevskaya, K Welch
and J Bryant*

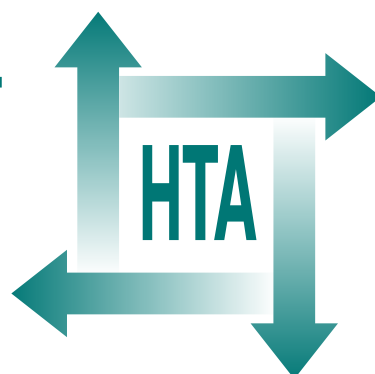Southampton Health Technology Assessments Centre (SHTAC),
Southampton, UK

*Corresponding author

Executive summary

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Background

Recombinant human growth hormone (rhGH) is licensed for short stature that is associated with growth hormone deficiency (GHD), Turner syndrome (TS), Prader–Willi syndrome (PWS), chronic renal insufficiency (CRI), short stature homeobox-containing gene deficiency (SHOX-D) and being born small for gestational age (SGA). The National Institute for Health and Clinical Excellence (NICE) guidance currently recommends rhGH treatment for children with GHD, TS, PWS or CRI, but does not cover SGA or SHOX-D.

Objectives

The aim of this report was to assess the clinical effectiveness and cost-effectiveness of rhGH compared with treatment strategies without rhGH for children with GHD, TS, PWS, CRI, SHOX-D and those born SGA. The report extends the previous review by actively searching for studies that report growth outcomes, body composition, biochemical markers or quality of life (QoL).

Methods

Data sources

The systematic review of clinical effectiveness used a priori methods that are described in the research protocol. We searched key databases (e.g. MEDLINE, EMBASE, NHS Economic Evaluation Database and eight others) for relevant studies from their inception to June 2009, limiting to the English language. Relevant conferences, bibliographies of included papers, our expert advisory group and manufacturers' submissions (MSs) to NICE were also consulted to identify any additional published or unpublished references. We developed an economic model using the best available evidence to determine cost-effectiveness in the UK.

Study selection

Two reviewers assessed titles and abstracts of studies identified by the search strategy, obtained the full text of relevant papers, and screened them against the inclusion criteria as defined in the research protocol. Any differences in opinion throughout the process were resolved through discussion.

Key inclusion criteria were:

- *patients* children with GHD, TS, PWS, CRI, SHOX-D or born SGA
- *treatment* rhGH
- *comparator* treatment strategies without somatropin
- *outcomes* height, height standard deviation score (HtSDS), growth velocity (GV) and SDS, body composition, biochemical markers, QoL, adverse events (AEs)
- *study type* randomised controlled trials (RCTs), systematic reviews.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and checked by a second. The quality of included studies was assessed using standard criteria. Criteria were applied by one reviewer and checked by a second, with differences in opinion resolved by discussion and involvement of a third reviewer where necessary.

Data synthesis

Clinical effectiveness studies were synthesised through a narrative review, with tabulation of results of included studies. Meta-analysis was not appropriate due to heterogeneity of study design and participants.

Economic model

A decision-analytical model was developed to estimate the cost-effectiveness of rhGH treatment compared with no treatment for a cohort of children with GHD, TS, PWS, SGA, CRI and SHOX-D. The model was based upon that developed in a previous Health Technology Assessment (HTA) report but was extended by including QoL factors. The perspective of the

analysis was that of the UK NHS and Personal Social Services (PSS). The model was informed by a systematic search of the literature to identify parameters on the natural history and epidemiology of the indicated conditions, health-related quality of life (HRQoL) and costs. The model estimated the lifetime costs and benefits of rhGH with discount rates of 3.5%. The intervention effect in terms of improvement of HtSDS was derived from the systematic review of effectiveness. The outcome of the economic evaluation is reported as cost per quality-adjusted life-year (QALY) gained and cost per centimetre gained.

Results

Number and quality of studies

Of the 674 references identified, 560 were excluded on inspection of their titles and abstracts. The full papers of 114 references were retrieved, of which 28 RCTs in 34 publications were included in the systematic review of clinical effectiveness. Overall, the studies were generally poorly reported and some were of short duration.

Summary of benefits and risks

None of the studies reported QoL measures, and reporting of AEs was limited. Only one of the included studies reported adult height (AH).

Growth hormone deficiency (one RCT)

Children in the rhGH group grew 2.7 cm/year faster than children in the untreated group and had a statistically significantly higher HtSDS after 1 year: -2.3 ± 0.45 versus -2.8 ± 0.45.

Turner syndrome (six RCTs)

Girls in one study grew an average of 9.3 cm more than untreated girls. In a study of younger children, the difference was 7.6 cm after 2 years. HtSDS values were statistically significantly higher in treated than in untreated girls.

Prader–Willi (eight RCTs)

Infants who received rhGH for 1 year grew significantly taller (6.2 cm more) than those in the untreated group in the only study to report change in height. Two studies reported a statistically significant difference in HtSDS in favour of rhGH. rhGH-treated patients had statistically significantly higher lean body mass (LBM) and lower body fat than untreated patients in three studies. Effects on body mass index (BMI) were mixed.

Chronic renal insufficiency (six RCTs)

Recombinant human growth hormone-treated children in a 1-year study grew an average of 3.6 cm more than untreated children. HtSDS was statistically significantly higher in treated than in untreated children in two studies.

Small for gestational age (six RCTs)

No RCTs met the original inclusion criteria for the review, so these were amended to include children from the age of 3 years with no catch-up growth, with no reference to mid-parental height. Only one out of the six included RCTs used the licensed dose; the others used doses two or three times higher. AH was approximately 4 cm higher in rhGH-treated people in the only study to report this outcome. AH-gain SDS was also statistically significantly higher in this study's rhGH group. Mean HtSDS was higher in treated than untreated patients in four other studies, significantly so in two of these.

SHOX deficiency (one RCT)

After 2 years of treatment, children were approximately 6 cm taller than the control group and HtSDS was statistically significantly higher in treated than in untreated patients.

Summary of cost-effectiveness

The systematic review of published economic evaluations identified two North American studies for children with TS and GHD and no studies conducted in the UK. The results of the two identified studies produced two very different estimates of cost-effectiveness, largely due to the choice of utility estimates and assumptions on effectiveness.

The systematic review of QoL identified only six studies, mostly of poor methodological quality and for small numbers of individuals. One reasonable study was found for GHD. An additional study was found, which estimated QoL utilities in the general adult population according to height, using the Health Survey for England. These studies suggested that there is likely to be a small gain in utility from rhGH.

Six of the seven manufacturers submitted evidence to be considered for this review. Five out of the six manufacturers collaborated and submitted essentially the same electronic model. The model developed was based upon the previous HTA report but was extended to consider longer-term outcomes in order to estimate cost-effectiveness in terms of QALYs. In the manufacturers' base case, the cost-effectiveness results for all conditions were less than £30,000 per QALY gained.

From the model we developed for this review, the incremental cost per QALY estimates of rhGH compared to no treatment were: £23,196 for GHD, £39,460 for TS, £135,311 for PWS, £39,273 for CRI, £33,079 for SGA and £40,531 for SHOX-D. A further analysis was run for PWS, which included a lifelong improvement in body composition of 1.8 BMI and an associated additional utility of 0.031. Under these assumptions, the cost-effectiveness of PWS reduced to £54,800 per QALY gained.

The effects of a range of parameter values for the economic model were evaluated in sensitivity analyses. The model results were found to be most sensitive to the discount rate used. All conditions, except PWS, were cost-effective for a willingness-to-pay threshold of £30,000 per QALY when the previous NICE discount rates of 6% for costs and 1.5% for benefits were used. The model results are also sensitive to treatment start age and length, compliance and utility gain. The probability sensitivity analysis (PSA) estimated the probability of each of the conditions to be cost-effective at £30,000 to be: 95% for GHD, 19% for TS, 1% for PWS, 16% for CRI, 38% for SGA and 15% for SHOX-D.

Discussion

The systematic review was restricted to RCTs because these provide the highest level of evidence for clinical effectiveness. However, very few of these reported either final height (FH) or QoL as outcome measures, most were only 1 or 2 years in length, and some had very few participants. We did not identify any RCTs that met the original inclusion criteria for children born SGA, so these had to be amended. Only one of the included trials used the licensed dose, so results from the other five could overstate the effectiveness of rhGH treatment for this patient group.

The QoL gains were highest for individuals with lower starting heights; for those with starting

height of less than < –2 HtSDS the QoL gain was minimal. For example, those with PWS had a starting height of –2 HtSDS, and so for this group of patients the health gain (in terms of height) is small; therefore, rhGH treatment has high incremental cost-effectiveness ratio (ICER) values compared with no treatment. Patients with PWS may experience an improvement in body composition due to rhGH treatment, and this is often the point of treatment rather than gain in height, but this was difficult to quantify, especially in the long term.

The cost-effectiveness results in the current report varied from those in the MS and the previous HTA report. The incremental costs reported are generally consistent between the three models. In general, the results, presented in terms of centimetres gained, are more favourable in the current analyses than in those in the previous HTA report. The ICERs in the MS are considerably more favourable than the current analysis, due to higher estimates of utility gain.

The current analysis has not considered other benefits in addition to height gain within the model, apart from as a scenario analysis for PWS. The base case does not include possible benefits from changes in body composition, such as reduced risk of diabetes or cardiovascular disease, which may result in increases in life expectancy. At this stage, these health gains would be purely speculative due to lack of data, and it is not possible to quantify them. It is also possible that there may be additional psychological benefits such as improved self-esteem.

Conclusions

The included studies reported statistically significantly larger HtSDS values for rhGH-treated children than untreated children with GHD, TS, PWS, CRI, SGA and SHOX-D. rhGH-treated children with PWS also showed statistically significant improvements in body composition measures compared with controls. The cost-effectiveness estimates from our model vary between conditions. Only GHD would be considered cost-effective according to a willingness-to-pay threshold of £20,000–30,000 per QALY gained. TS, CRI, SGA and SHOX-D have ICERs between £33,000 and £40,500 per QALY gained. PWS has an ICER of between £55,000 and £135,000 per QALY gained, depending on assumptions.

Key research priorities

- Longer studies beyond 2 years, reporting near-FH or final AH.
- A standardised QoL assessment specifically designed for children and adults, to be used in future RCTs and QoL studies.
- Good-quality trials of rhGH in children born SGA, where the children included and the dose administered match the licensing criteria.
- Good-quality studies of the long-term effects of rhGH on body composition, psychological benefits, long-term morbidities (such as diabetes or cardiovascular disease) and life expectancy, particularly for individuals with PWS.

Publication

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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