Overview of Recombinant Human Growth Hormone for Treatment of Turner Syndrome: Systematic Review and Economic Evaluation
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December 2007

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CADTH takes sole responsibility for the final form and content.
Recombinant Human Growth Hormone for Treatment of Turner Syndrome: Systematic Review and Economic Evaluation

Technology and Condition
Recombinant human growth hormone (rhGH) for treatment of Turner syndrome (TS).

Issue
Given the high cost of rhGH treatment and the evolving evidence base for its clinical effect in patients with TS, policy makers need evidence to inform reimbursement decisions about rhGH.

Methods and Results
A systematic review was conducted to identify randomized controlled trials (RCTs) and comparative observational studies comparing rhGH with placebo or no treatment in patients with TS. The outcomes of interest were growth, adverse events (AEs), and quality of life (QoL). A meta-analysis was conducted where appropriate. Primary economic analyses were also undertaken, using the perspective of the public health care system and a lifetime horizon. Six RCTs and nine observational studies were included, ranging in duration from one to eight years. The included studies showed that rhGH treatment accelerates growth and results in improvement in height. No serious AEs were reported in the included studies. QoL data, derived from two RCTs, were variable precluding any conclusion about rhGH’s influence on QoL. Base case economic analysis showed that the incremental cost-effectiveness ratio (ICER) of rhGH treatment versus no treatment was C$23,630 per centimetre of final height improvement or C$243,078 per quality-adjusted life year (QALY) gained.

Implications for Decision Making

- **Treatment with rhGH has a demonstrated impact on final height but its effect on QoL is uncertain.** The available evidence suggests that, compared with patients receiving placebo or no treatment, patients who are treated with rhGH experience accelerated growth and improvement in final height. Treatment appears to be safe with no serious AEs and few, if any, AEs reported. QoL data, reported in two studies, were variable and inconclusive.

- **For the average patient, rhGH is cost effective if a payer is willing to pay more than C$200,000 for a QALY.** However, from an ethics perspective, the provision and funding of rhGH could be supported until those with TS reach the lower end of the normal adult height range.

- **Publicly funding rhGH treatment will require additional investment.** If it were assumed that all TS patients aged 10 to 15 years were eligible for rhGH therapy, the corresponding annual budget impact for covering ~400 patients across Canada would be C$11.3 million. The more likely scenario would be that 40% to 50% of eligible patients would receive treatment, with a proportionate decrease in expenditure.

This summary is based on a comprehensive health technology assessment available from CADTH’s web site (www.cadth.ca):
1 Introduction

Turner syndrome (TS), which is a chromosomal disorder in females, results from the absence of all or part of a normal second sex chromosome. The prevalence of TS is 1 in 2,500 to 1 in 3,000 live female births. The estimated number of cases of TS (from birth to 12 years old) in Canada is 660 to 792. There does not seem to be an increased risk of TS among specific racial or ethnic groups or among older mothers.

Because sex chromosomes play a role in the development of reproductive tissues and organs, mutations of these chromosomes cause several effects, with short stature being the most common (in 88% to 100% of those diagnosed). From birth, most patients with TS tend to be shorter than those without TS. This trend continues until they reach adult height. The mean final heights of patients with TS who do not receive treatment ranges from 136.7 cm in Japan to 146.9 cm in Germany. Girls with TS are approximately 20 cm shorter than those with normal height in their ethnic-specific population, although there may be individual variation due to the height of both parents, age of onset of puberty, nutritional status, and social background.

The diagnosis of TS should be based on physical features and chromosomal analysis. The management of TS combines ongoing medical assessment and evaluation at appropriate ages. The standard treatment for TS is recombinant human growth hormone (rhGH) alone or rhGH with estrogen or oxandrolone. rhGH is usually administered subcutaneously at doses between 0.3 mg/kg/week and 0.375 mg/kg/week. The dose is titrated according to the patient’s growth response. Although the optimal age for starting rhGH therapy has not been established, rhGH is generally prescribed from the time of diagnosis until growth is complete.

rhGH is injected subcutaneously at night via a syringe or a pen injector. Monitoring every four to six months is recommended to assess efficacy, compliance, and dose adjustment. rhGH is discontinued when a final adult height is achieved or if the patient chooses to stop taking the medication sooner.

<table>
<thead>
<tr>
<th>Table 1: Available rhGH products in Canada* and price†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Humatrope</td>
</tr>
<tr>
<td>Humatrope INJ</td>
</tr>
<tr>
<td>Humatrope</td>
</tr>
<tr>
<td>Humatrope</td>
</tr>
<tr>
<td>Saizen</td>
</tr>
<tr>
<td>Saizen</td>
</tr>
<tr>
<td>Saizen</td>
</tr>
<tr>
<td>Nutropin</td>
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<tr>
<td>Nutropin</td>
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<tr>
<td>Nutropin</td>
</tr>
<tr>
<td>Nutropin</td>
</tr>
<tr>
<td>Serostim</td>
</tr>
<tr>
<td>Serostim</td>
</tr>
</tbody>
</table>

DIN=drug identification number; rhGH=recombinant human growth hormone.
*Data source: Drug Product Database.
†Calculated based on net price to wholesalers according to PPS Pharma Buyers Guide.
Health Canada has approved four forms of rhGH (or somatropin): Humatrope® (Eli Lilly), Saizen® (Serono), Nutropin® (Roche), and Serostim® (Serono). The first three are indicated for use in TS and are available in various dosage forms, compositions, packages, and prices (Table 1). The formulary status of the products varies between provinces and programs.

The price of Humatrope (6 mg/vial) in the Alberta Health and Wellness Drug Benefit Listing is C$301.02 (i.e., C$50.17/mg). Given that the dose is weight-based (e.g., 0.3 mg/kg/week), rhGH treatment would cost C$14,088 per year for a five-year-old girl to C$32,871 per year for a 12-year-old girl. The underlying assumed weight for the five- and 12-year-old girls is 18 kg and 42 kg respectively.

2 Objectives

This report assesses the clinical effectiveness and cost-effectiveness of rhGH therapy for TS and addresses the following questions:

- Compared with no therapy, what is the clinical effect of rhGH for the treatment of the short stature associated with TS?
  - What is the effect of rhGH therapy on growth outcomes?
  - What are the adverse effects (short- and long-term) associated with rhGH therapy?
  - What is the effect of rhGH therapy on quality of life (QoL)?
- What is the cost-effectiveness of rhGH for the treatment of short stature associated with TS in the Canadian context?
- What is the budget impact of publicly reimbursing rhGH treatment for children with TS?

3 Clinical Review

Literature Search Strategy

Systematic literature searches were conducted for the clinical review. Several databases were searched, including Medline, EMBASE, BIOSIS Previews, CINAHL, PsycINFO, and the Cochrane Library. Results were limited to publications from 1980 onwards, because rhGH has been available only since 1985.

Selection Criteria and Methods

Studies were selected for inclusion if they satisfied the following criteria:

- Study design: randomized controlled trial or comparative observational study
- Population: females diagnosed with TS
- Intervention: rhGH
- Comparator: placebo or no treatment
- Outcome: growth (final height, interim height, growth velocity), adverse events, and QoL.

Studies with <20 patients or rhGH treatment <1 year were excluded, because they are unlikely to provide robust results.
Two reviewers independently selected trials for inclusion. Differences in decisions between reviewers were resolved by consensus.

**Results**

Of 527 relevant citations that were identified from the original literature search, 81 potentially relevant reports were retrieved. Of these, 19 reports were selected for inclusion: 10 reports describing six RCTs and nine reports describing nine comparative observational studies.

**Study Characteristics**

Of the six RCTs, five\textsuperscript{14-18} were multi-centre trials, and one\textsuperscript{19} did not mention the number of centres. The number of patients included in the studies ranged between 40 and 232, and treatment duration ranged from one to seven years. The mean age of patients in the RCTs at baseline ranged between 8.9 and 10.9 years. Bone age and height ranged from 7.2 to 8.9 years and 114 to 122 cm respectively in five RCTs\textsuperscript{14-17,20}. The karyotype (45,X) of the patients was reported in four RCTs\textsuperscript{14,17,19,20}. The percentage of patients having the 45,X karyotype varied between 55% and 95%.

Using a combination of the Jadad scale and the Hailey scale to judge the reporting quality, two RCTs\textsuperscript{14,15} were judged to be of high quality, three RCTs\textsuperscript{16-18} of good quality, and one RCT\textsuperscript{19} of fair quality.

With respect to the nine comparative observational studies comparing rhGH treatment with no rhGH treatment in patients with TS, four\textsuperscript{21-24} were prospective studies and five\textsuperscript{25-29} were retrospective studies. The number of patients ranged between 26 and 123, and the treatment duration ranged between two and eight years. The mean age of patients in the comparative observational studies ranged between 10.2 and 21.7 years.

Using a combination of the Jadad scale and the Hailey scale to judge the reporting quality of the comparative observational studies, one study\textsuperscript{21} was judged to be of good quality, six \textsuperscript{21-23,25,28,29} of fair quality, and two\textsuperscript{26,27} of poor quality.

**Data Analyses and Synthesis**

a) **Growth and Height**

Different investigators assessed growth using different variables to assess patients in the studies. These included final height (FH), height standard deviation score (HSDS), change in HSDS (ΔHSDS), growth velocity (GV), and growth velocity SDS (GVSDS).

Five\textsuperscript{14-18,30} of the six RCTs reported growth-related data. Long-term (mean±SD=5.7±1.6 years after randomization) data were available from a Canadian RCT.\textsuperscript{14} In this trial, patients receiving rhGH treatment had a significantly higher growth compared with patients not treated with rhGH. The mean differences (MD) and 95% confidence intervals (CI) were 6.50 cm (4.28, 8.72) for final height, 1.00 (0.67, 1.33) for HSDS, and 1.30 (1.11, 1.49) for ΔHSDS. The mean final height in rhGH-treated patients was 147.5 cm. Johnston \textit{et al}.\textsuperscript{16} and Kollmann \textit{et al}.\textsuperscript{17} showed that ΔHSDS was greater for patients treated with rhGH for one year compared with patients who did not receive rhGH.

GV and GVSDS were higher for patients treated with rhGH compared with patients not receiving rhGH (Tables 2 and 3), hence favouring the use of rhGH in patients with TS. Rosenfeld\textsuperscript{18} showed that the GV and GVSDS were higher if the treatment regimen included oxandrolone. The GV in this
trial (expressed as mean±SD) was 6.60±1.20 for rhGH alone, 9.80±1.40 for rhGH in combination with oxandrolone, 3.8±1.1 for no rhGH, and 7.6±1.5 for oxandrolone alone.

The RCTs show that rhGH treatment accelerates growth and results in improvement in height.

### Table 2: MD in GV determined from RCTs comparing rhGH treatment versus no rhGH treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients</th>
<th>Patient Groups</th>
<th>Observation Period (years)</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian</td>
<td>86</td>
<td>All groups</td>
<td>1</td>
<td>3.80 (3.29, 4.31)</td>
</tr>
<tr>
<td>Canadian</td>
<td>69</td>
<td>All groups</td>
<td>2</td>
<td>1.80 (1.27, 2.33)</td>
</tr>
<tr>
<td>Quigley</td>
<td>90</td>
<td>rhGH 0.27 mg/kg/week group and control</td>
<td>1</td>
<td>2.40 (1.93, 2.87)</td>
</tr>
<tr>
<td>Quigley</td>
<td>86</td>
<td>rhGH 0.36 mg/kg/week group and control</td>
<td>1</td>
<td>2.60 (2.14, 3.06)</td>
</tr>
<tr>
<td>Rosenfeld</td>
<td>35</td>
<td>Groups receiving oxandrolone</td>
<td>1</td>
<td>2.20 (1.24, 3.16)</td>
</tr>
<tr>
<td>Rosenfeld</td>
<td>35</td>
<td>Groups not receiving oxandrolone</td>
<td>1</td>
<td>2.80 (2.04, 3.56)</td>
</tr>
</tbody>
</table>

CI=confidence interval; GV=growth velocity; MD=mean difference; RCT=randomized controlled trial; rhGH=recombinant human growth hormone.

### Table 3: MD in GVSDS from RCTs comparing rhGH treatment versus no rhGH treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients</th>
<th>Patient Groups</th>
<th>Observation Period (years)</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian</td>
<td>86</td>
<td>All groups</td>
<td>1</td>
<td>3.2 (2.65, 3.75)</td>
</tr>
<tr>
<td>Canadian</td>
<td>69</td>
<td>All groups</td>
<td>2</td>
<td>1.60 (1.02, 2.18)</td>
</tr>
<tr>
<td>Rosenfeld</td>
<td>35</td>
<td>Groups receiving oxandrolone</td>
<td>1</td>
<td>2.20 (1.19, 3.21)</td>
</tr>
<tr>
<td>Rosenfeld</td>
<td>35</td>
<td>Groups not receiving oxandrolone</td>
<td>1</td>
<td>3.20 (2.47, 3.93)</td>
</tr>
</tbody>
</table>

CI=confidence interval; GVSDS=growth velocity standard deviation scores; MD=mean difference; RCT=randomized controlled trial; rhGH=recombinant human growth hormone.

Seven of the nine comparative observational studies reported growth-related data. Three prospective studies showed that the final height was significantly higher in rhGH-treated patients compared with those who did not receive rhGH. When these studies were pooled, the WMD (95% CI) was 5.86 (4.30, 7.41), again favouring rhGH treatment.

Three retrospective studies showed that the final height was higher in the rhGH-treated patients compared with patients not receiving rhGH. The difference was statistically significant in one study but not in the other two.

Two prospective studies showed that the HSDS was significantly higher in the rhGH-treated patients compared with patients not receiving rhGH. When these studies were pooled, the WMD (95% CI) was 1.08 (0.78, 1.38), favouring rhGH treatment. Two retrospective studies also showed that the HSDS was higher in the rhGH-treated patients compared with patients not receiving rhGH. The difference was statistically significant in one study but not in the other.

Naeraa et al. showed that there was no difference in growth velocity [MD (95% CI)=0.00 (−1.50, 1.50)]. Dacou-Voutetakis et al., however, showed that the GVSDS was higher in patients treated with rhGH compared with patients not treated with rhGH.
The comparative observational studies show that rhGH treatment results in improvement in height.

b) Quality of Life
QoL data were available from two RCTs. No QoL data were available in the comparative observational studies. Because the data were sparse, conclusions cannot be made regarding QoL improvement in those treated with rhGH compared with those not treated with rhGH.

c) Adverse Events
Not all RCTs reported adverse events (AEs). The Canadian RCT noted significantly higher rates of AEs (surgical procedure, otitis media, ear disorder, joint disorder, respiratory disorder, and sinusitis) in the rhGH group compared with the control group (not treated with rhGH). No mortality was reported in the rhGH group. One patient in the control group died because of a ruptured aortic aneurysm.

Quigley et al. reported serious AEs in 5% of patients treated with rhGH. Rosenfeld et al. reported that there were few AEs in patients receiving rhGH alone. Two patients developed transient edema, one developed acne, and one noted increased weight.

Five comparative observational studies reported AEs. Bakalov et al. did not find any difference in the prevalence or incidence of fracture between the two groups. Naeraa et al., Pasquino et al., and Taback et al. reported that no serious side effects were observed during treatment. Hochberg et al. reported that rhGH therapy was well tolerated, with no apparent AEs.

Discussion
The results from RCTs and comparative observational studies suggest that rhGH is effective in improving growth velocity and final height. The Canadian RCT (mean follow-up of 5.7 years) showed that the final height was 6.5 cm greater in patients treated with rhGH compared with those who did not receive rhGH. The treated patients had a mean final height of 147.5 cm. Pooled results from three prospective observational studies showed that the final height was approximately 5.9 cm greater in patients treated with rhGH compared with those who did not receive rhGH.

The height gain in patients with TS is variable, and its clinical importance is debatable. There is no evidence that can be used to determine whether rhGH treatment improves QoL and if an increase in height correlates with improved QoL.

4 Economic Review

Literature Search
The following bibliographic databases were searched: Medline, EMBASE, BIOSIS Previews, and CINAHL. Parallel searches were run in the Health Economic Evaluations Database (HEED) and the Cochrane Library. Results were limited to publications from 1980 onwards, because rhGH has been available only since 1985.
Selection Criteria and Methods
Studies were eligible for inclusion if they satisfied the following selection criteria:

- Study design: full (e.g., cost-minimization, cost-effectiveness, cost-utility, or cost-benefit analysis) or partial (e.g., cost-analysis, cost-comparison, or cost-consequence analysis) economic study
- Population: females diagnosed with TS
- Intervention: rhGH
- Comparator: placebo or no treatment
- Outcomes: cost of rhGH treatment, growth, increased QALYs, incremental cost per centimetre of height gained, incremental cost per QALY gained.

Two reviewers independently selected abstracts according to the criteria. Both reviewers reviewed the full text of articles, and disagreement was resolved by consensus.

Results
Of 102 citations identified in the literature search, four were deemed suitable for scrutiny. One UK study\(^3\) satisfied all criteria and was included in the review. The included report\(^3\) was published by the UK National Institute for Clinical Excellence (NICE). It examined the clinical and economic benefits of rhGH therapy for five indications, including TS.

The UK report assumed two base cases in terms of final height gained: base case 1 (4.8 cm) and base case 2 (4.4 cm). The corresponding incremental cost-effectiveness ratios (ICERs) were £15,997 (C$35,991 in 2000 Canadian dollars) or £17,429 (C$39,213) per centimetre for cases 1 and 2 respectively.

Discussion
Although the UK study reported the value of rhGH treatment for patients with TS in terms of incremental cost per centimetre gained, it did not perform a cost-utility analysis (CUA). Because QoL is an important outcome, a CUA would have provided more useful information.

5 Economic Analysis
Model-based cost-effectiveness analyses and CUAs were performed because of the clinical benefit of rhGH treatment. It has been shown to improve the final height of girls with TS. This is thought to be associated with an increase in QoL. In a cost-effectiveness analysis (CEA), the economic value of rhGH treatment for TS was quantified in incremental cost per centimetre of final height gained. In a CUA, outcomes with one type of health-related preference were measured.

A hypothetical cohort of girls who were diagnosed with TS, whose rhGH treatments were started at age 10 (as in the Canadian RCT), was assumed. Comparators were rhGH treatment and no treatment. Based on the Canadian RCT,\(^1\) the duration of treatment was assumed to be six years.

For the CUA, the best data came from a Dutch study\(^3\) that quantitatively estimated reductions in QoL due to short stature. This study found that a patient with TS on average would trade 4.2% of her lifetime to achieve normal height. A time horizon of 80 years (the mean life span of Canadian
women) and achievement of normal height would result in an overall gain of 3.36 QALY (with no discounting) for a girl with TS.

Only the direct costs associated with rhGH treatment were considered (i.e., drug costs and the incremental cost of health services required). The total costs for the hypothetical cohort of girls with TS who received rhGH treatment at age 10 and completed treatment at age 15 were C$153,593 with discounting (C$172,435 without discounting). This value represents only the incremental costs of a patient with rhGH treatment versus without treatment and excludes the costs of health services that are common to both scenarios.

For the CEA, the results from the Canadian RCT were used (the mean height of a girl with TS was 147.50 cm with rhGH therapy and 141.00 cm without therapy). Therefore, the final height gained over her lifetime was 6.50 cm. For the CUA, it was assumed that QoL stayed the same until rhGH therapy was completed. Thus, the QALY per year was the same from birth to 15 years old (the period before GH therapy is completed). Compared with a patient without rhGH, a girl with TS who completed rhGH treatment would gain 0.042 QALY per year from age 16 years to 81 years (the age we assumed to be the average life expectancy of patients with TS), resulting in 0.63 QALY (discounted) or 2.77 QALYs (not discounted) over her lifetime.

Thus, the application of this CUA’s results requires caution. It is difficult to conclude that rhGH therapy for TS is cost-effective unless the payer is willing to pay >C$200,000 for a QALY. It was estimated that to reach C$50,000 per QALY, a girl with TS would have to be willing to trade 20.4% of her lifetime for final height improvement, instead of the 4.2% in our base case, or the unit cost of somatropin would have to drop to C$8.92 per milligram instead of the current price of C$42.36 per milligram.

6 Limitations

Clinical Limitations
There were restrictions as to which patients were eligible to participate in the RCTs. Hence, the results may not be generalizable to all patients with TS.

Economic Limitations
Because neither rhGH treatment nor no treatment has an impact on mortality in patients with TS, the health-related quality of life (HRQL) becomes an important outcome. No RCTs have adequately addressed this issue, so the following questions remain to be answered in future studies: Is short stature a disability? Does short stature impair the QoL of a patient with TS? Are differences in QoL undetected because of a lack of suitable instruments?
7 Health System Implications

Population Impact
Each year there are 66 new cases of TS in Canada, with most cases in Ontario. Assuming that girls with TS at age 10 to 15 years all receive rhGH therapy, the total population would be 396 girls with TS in Canada. Therefore, each year 396 girls with TS qualify for publicly funded rhGH therapy.

Budget Impact
A budget impact analysis was undertaken to examine the financial impact of publicly funding rhGH treatment for patients with TS in Canada. For this analysis, it was assumed that the duration of rhGH treatment was six years.

In general, fully reimbursing rhGH therapy for patients with TS led to increased budgets for all jurisdictions except Prince Edward Island, Yukon Territory, the Northwest Territories, and Nunavut, where there are no cases of TS according to the estimation. If a full reimbursement policy was started in 2007, the one-year budget would be from C$0.17M to C$4.45M, depending on the province. Within a three- or five-year horizon, the total budget at the provincial level was estimated to range from C$0.49M to C$12.72M or C$0.78M to C$20.23M respectively. One assumption underlying these calculations was that all girls with TS aged 10 to 15 years were diagnosed and received rhGH therapy. If a more realistic scenario is assumed, so that 40% to 50% of patients with TS receive treatment, then the budget impact would be 40% to 50% of what has been stated.

8 Conclusions

The evidence suggests that rhGH treatment is effective in improving growth and final height, but there is no evidence about whether rhGH treatment improves QoL. In RCTs and comparative studies, AE data were sparsely reported, and there was variability. Long-term studies of high quality are needed to determine the benefits and drawbacks of rhGH treatment.

The one economic study that was identified showed that the cost per centimetre of final height gain with rhGH was >£10,000 (C$22,498) compared with no treatment, but it came to no conclusion as to whether rhGH therapy is cost-effective.

Our economic evaluation showed that for the average patient with TS, rhGH treatment is unlikely to be considered cost-effective unless the payer is willing to pay >C$200,000 to obtain a QALY. Future research is needed to generate more robust data.

Distributive and social justice arguments could support the provision of publicly funded rhGH to persons with TS, and particularly support the funding of such therapy until affected individuals achieve the lower end of the normal adult height range.

Funding rhGH therapy for patients with TS will increase the budgets of government drug plans, hence opportunity costs should be considered.
9 References


