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Recombinant human growth hormone for children born small for gestational age: Meta-analysis confirms the consistent dose-effect relationship on catch-up growth

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ABSTRACT. ***Background:*** **The optimal treatment regimen of recombinant human GH (r-hGH) for short children born small for gestational age (SGA) is still under discussion.** ***Methods:*** **A meta-analysis was performed of existing clinical trials that investigated the treatment of r-hGH in short children diagnosed SGA or with intrauterine growth retardation to determine the relationship between the daily r-hGH dose (placebo/no treatment; 0.033 mg/kg/day; 0.067 mg/kg/day) and the effect on growth [change in height-SD score (SDS) for chronological age]. A mathematical model describing the dose-response relationship was produced, and growth response (gain in height-SDS) to 2 yr of r-hGH 0.033 mg/kg/day [somatropin (rDNA origin) for injection; Serono] was estimated and compared with the response to other r-hGH formulations.** ***Results:*** **The relationship between r-hGH dose and 2-yr growth response was described by an equation. The equation yielded a mean difference in height-SDS gain of 0.48 (0.35) between r-hGH 0.033 and 0.067 mg/kg/day in favor of the higher dose. The height-SDS gain after 2 yr of Serono r-hGH formulation, 0.033 mg/kg/day was estimated as 1.2. Comparison of this estimate to the growth response to 2-yr treatment at 0.033 mg/kg/day of other r-hGH formulations (mean difference in height-SDS 0.05, lower limit of the 95% confidence interval=-0.15) confirmed that growth response to Serono r-hGH formulation 0.033 mg/kg/day is an inferred response estimated to be within the range of observed responses to a (non-Serono formulation) r-hGH dose of 0.033 mg/kg/day.** ***Conclusion:*** **There is a clear dose-response relationship for r-hGH in the treatment of short children born SGA and the analysis confirmed that treatment with Serono r-hGH formulation 0.033 mg/kg/day should provide a meaningful therapeutic response.**

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INTRODUCTION

The 10-15% of children who are born small for gestational age (SGA) and lack post-natal catch-up growth achieve a reduced adult height compared with the general population (1-3). Over the past 15 yr, substantial clinical evidence has been generated supporting the efficacy of recombinant human GH (r-hGH) in the treatment of growth retardation in children born SGA who fail to demonstrate catch-up growth during early childhood (4-11). This evidence has resulted in approval of r-hGH treatment for this indication in both the USA and the EU.

Studies have used a range of doses of r-hGH for this indication but there is still discussion on what would be the treatment regimen for optimal long-term benefit. Most experts believe that the optimum results are obtained with high doses of r-hGH (i.e. 0.067 mg/kg/day). This is supported by clinical trials demonstrating that children treated with this dose achieve a height in the normal range for age and sex within 3 yr. Some clinical benefit may also be obtained with a dose that is close to that used in the treatment of GH deficiency (0.033 mg/kg/day) (6, 8, 10, 12). A few studies have suggested that there is a dose-response effect for r-hGH treatment and growth rate in children born SGA with insufficient post-natal growth catch up (6, 8, 10). Furthermore,

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the dose of GH has been shown to be the most important predictor for growth response during the 1st yr of treatment. During the 2nd yr of treatment, age at the time of treatment onset was the most important predictor of growth response, with a smaller response in older children, and GH dose was the second most important factor (13).

To investigate how consistent and predictable the difference in response to various r-hGH doses is in a larger population of patients, we first conducted a meta-analysis aimed at quantifying the relationship between r-hGH dose and growth response using data from a large pool of studies and tried to model this correlation mathematically. In a second step, the obtained mathematical equation was used to calculate an estimate of the efficacy of a 0.033 mg/kg/day dose that has not previously been tested in prospective clinical trials for the treatment of short children born SGA for a particular formulation of r-hGH [somatropin (rDNA origin) for injection, Serono International, Geneva, Switzerland]. However, results are available from 2 clinical trials using a higher dose of this r-hGH formulation (0.067 mg/kg/day) in the treatment of short children born SGA that could be used as a point of reference. As a third step, a simulation exercise was performed to provide a more accurate estimate of the efficacy, an estimate of the treatment effect (i.e. the difference to be expected between Serono r-hGH formulation and other r-hGH preparations at the 0.033 mg/kg/day dose) and confidence intervals (CI) on this treatment effect.

As not all clinical trials have confirmed the dose-response relationship of growth after r-hGH treatment, the aim of this analysis was to establish a mathematical model for the dose-response relationship of the gain in height-SD score (SDS) after 2 yr of treatment with r-hGH in short children born SGA, which would be based on the data from a meta-analysis of clinical trials. This equation was then used to provide a point estimate and 95% CI of the estimated gain in height-SDS if the Serono-sponsored clinical trials had been performed with an r-hGH dose of 0.033 mg/kg/day (as opposed to a dose of 0.067 mg/kg/day). Finally, the intention was to assess if this estimate of the gain in height-SDS after treatment with 0.033 mg/kg/day of r-hGH (Serono formulation) in short children born SGA was similar to the effect of other r-hGH preparations given at the same dose for the same indication. This analysis was carried out to meet the European Agency for the Evaluation of Medical Products (EMEA) requirements for a dose rationale as part of the submission file to substantiate the data for registration purposes. The methodology used is robust and appropriate. In particular, the strength of this method is that the simulation exercise provides a more accurate estimate with CI.

METHODS

Investigational plan and methodology

For the first part of the study, a meta-analysis was performed of existing clinical trials conducted by Serono and other published clinical trials that investigated the treatment of r-hGH in short children diagnosed SGA or with intrauterine growth retardation (IUGR) [defined as birth length and/or birth weight equal to, or below, the 10th percentile of gestational age-related growth curve standards, except in one study (14), where IUGR was mentioned but not defined]. This analysis was undertaken to determine the relationship between the daily dose administered and the effect on growth as defined by the change in height-SDS for chronological age. The aim was to include all randomized clinical trials that used any of the following 3 dose regimens: placebo or no treatment; 0.033 mg/kg/day or equivalent dose expressed in IU instead of mg, or as a dose per m^2 instead of per kg; 0.067 mg/kg/day or equivalent dose. The inclusion of other studies, using different doses of GH, was considered. However, there are a limited number of studies examining the effect of other doses of GH on growth response, involving a limited number of patients. Furthermore, differences in study design and duration would have increased the variability of the results of the analysis. Therefore, it was decided to limit the analysis to studies using 0.033 mg/kg/day or 0.067 mg/kg/day.

Only studies that provided data on the gain in height-SDS over 2 yr of treatment were selected. This choice was made to provide the best balance between the length of the treatment period and the size of the data set used to compare Serono-sponsored studies with non-Serono studies.

Search strategy

The following databases were searched, MEDLINE (Ovid 1966-March 2004), Cochrane Library and EMBASE (Ovid 1980-March 2004). The search strategy used both key-words and MeSH term searches and took the form of (GH and synonyms) and (SGA or IUGR and synonyms) combined with a search filter specifically designed to identify randomized controlled trials. Grey literature was sought through searching a number of Internet sites including health technology assessment agencies, EMEA and US Food and Drug Administration (FDA) websites. No language restriction was applied to the searches. For the studies sponsored by Serono, data were extracted from the clinical trial reports.

Study selection and data extraction

Two reviewers independently scanned all the titles and abstracts and identified potentially relevant articles to be retrieved. Where there was uncertainty, full text copies of papers were obtained. Studies were considered eligible if they met the following criteria: design, randomized controlled clinical trials (RCT); population, children diagnosed with growth retardation and SGA or IUGR; intervention and comparison, r-hGH alone, r-hGH dose comparison, or r-hGH *vs* placebo/no intervention. Outcomes sought included change in height and height-SDS. Data were abstracted by a single reviewer and checked by a second reviewer.

Quality assessment

The methodological quality of included studies was assessed in terms of the method of randomization, adequacy of allocation concealment, blinding of outcome assessment, and proportion of patients lost to follow-up. The overall level of methodological bias was scored using a modified Jadad scale (15). Disagreements in assessment between reviewers were resolved by consensus.

Statistical analyses

The studies selected are detailed in Table 1. The studies sponsored by Serono used an r-hGH dose of 0.067 mg/kg/day. In all non-Serono studies selected, a dose of either 0 (no treatment), 0.033 or 0.067 mg/kg/day was used. Using an analysis of covariance (ANCOVA) with baseline height-SDS as a covariate, an equation was obtained modeling the gain in height-SDS as a function of the dose in mg/kg/day. The regression process was weighted by the size of the study.

Using the equation obtained, the gain in height-SDS in the Serono-sponsored studies using a dose of 0.067 mg/kg/day was derived to estimate the coefficients required for assessing the correlation between the 0.033 mg/kg/day and 0.067 mg/kg/day doses of r-hGH. By pooling the results from the Serono-sponsored and the non-Serono studies, these results were then considered to represent 0.033 mg/kg/day estimates.

For most studies in the analysis dataset created, an estimate of the SD was available (some *via* transformation from the SE). However, these estimates were time specific and not on the response variable, which is a gain in height-SDS from baseline to 2 yr; therefore, the variance in the gain in height-SDS was needed in order to define the correlation between the baseline height-SDS and the height-SDS measured at 2 yr. Finally, proc.mixed in SAS was applied on the data in which the change in height-SDS was the response and the 2 covariates were baseline height-SDS and the type of study (i.e. Serono-sponsored study or non-Serono study). Using this simulation process, the 90 and 95% CI for the study difference were calculated. The lower limit of these CI was used to assess non-inferiority.

RESULTS

A total of 112 publications were initially identified from searches. Based on title and abstract, 30 were deemed suitable for full paper assessment. Of these, 10 did not meet the inclusion criteria, 9 were duplicate publications, 4 were observational-registry studies, and 1 was a congress abstract with insufficient information. Five publications remained that described the results of 8 trials that met the clinical inclusion criteria. Four trials were published individually (12, 14, 16, 17) and the results of 4 others were compiled in 1 publication (8). For the 2 Serono-sponsored

Table 1 - *Features of studies selected for the meta-analysis, patient characteristics and effect of recombinant-human GH (r-hGH) on height-SD score (SDS).*

Publication	Design	Mean (SD) age at baseline	Mean (SD) height -SDS at baseline	Patients, no.	Gender M/F	r-hGH doses (mg/kg/day)	Mean gain in height-SDS
Van Pareren, 2003 (12)	Randomized Double-blind Not controlled	8.1 (1.9)	–3.0 (0.7)	28 26	18/10 NA	0.033 0.067	1.4 1.7
De Zegher, 1996 (8) (Meta-analysis of four studies) Belgium, Germany, Scandinavia	Randomized Open label Untreated control group	4.9 (0.1)	–3.6 (0.1)	38 38 54	NA	0 0.033 0.067	0.12 1.13 2.11
France	Randomized Double-blind Placebo-controlled	5.6 (0.1)	–3.0 (0.1)	9 49 40	NA	0 0.033 0.067	0.17 1.04 1.33
Rosilio, 1997 (14)	Open label	9.5 (0.9)	–2.6 (0.5)	30	21/9	0.067	1.28
Leger, 1998 (16)	Open label	6.1 (1.9)*	–3.6 (0.8)	14	8/6	0.067	1.7
Bundak, 2001 (17)	Randomized Controlled	4.3 (1.7) 5.3 (1.3)	–2.7 (1.4) –3.0 (0.5)	10 16	4/6 4/12	0 0.067	0.08 1.1
Study 4001, 2002	Randomized Open label	4.6 (1.8) [T] 4.5 (1.9) [C]	–3.3 (0.6) [T] –3.2 (0.9) [C]	50 [T] 50 [C]	26/24 [T] 25/25 [C]	0.067 [T] 0.067 [C]	1.68 [T] 1.52 [C]
Study 6283, 2003	Randomized Open label	3.4 (0.9)	–3.6 (0.6)	58	28/30	0.067	2

[T] and [C] are 2 treatment groups within the same study. *Value is mean (SEM). M: males; F: females; NA: not available.

trials included in the analysis, the data from the full clinical trial reports were used (Table 1).

Study characteristics

Across the 10 trials, a total of 510 patients were randomized to receive r-hGH, at a dose of 0.033 or 0.067 mg/kg/day, or no active treatment. One hundred and fifteen children received r-hGH 0.033 mg/kg/day, 338 received r-hGH 0.066 mg/kg/day, and 57 received no active treatment. All trials provided results from at least 2-yr treatment. Mean age at entry across trials was 5.6 yr and the mean height-SDS at start of treatment was –3.2 SD. There were insufficient trials to assess publication bias.

Regression of change in height-SDS vs *dose*

An overview of mean change in height-SDS and dose of each study is documented in Table 1. From these results, the observed mean (SD) change in height-SDS was 1.60 (0.33) with the 0.067 mg/kg/day dose, and 1.19 (0.19) with 0.033 mg/kg/day. Therefore, the observed mean (SD) difference in height-SDS between the 2 doses was 0.41 (0.52).

The results of the ANCOVA regression analysis are summarized in Table 2, where β1 and β2 are the regression coefficients (i.e. 44.02 and –305.59) for the dose and dose-squared terms, respectively. Based on this quadratic equation, the calculated mean (SD) difference in height-SDS between the 2 doses was 0.48 (0.35).

The results indicate that the effect of dose on the change in height-SDS after 2-yr treatment is statistically significant. Figure 1 demonstrates that the quadratic function provided an adequate fit to the data, and it was therefore selected as the most appropriate mathematical model to describe the dose-response relationship.

Translation to account for differing doses

The results of the translation of the 0.067 mg/kg/day data from Serono-sponsored studies into an estimate of efficacy at a 0.033 mg/kg/day dose are given in Table 3. The translation exercise gives estimates of a change in height-SDS of 1.06, 1.22, and 1.54 with the lower 0.033 mg/kg/day dose for the 3 patient populations in the Serono-sponsored studies.

Results of simulation

Based on this quadratic model, the estimated efficacy of a 0.033 mg/kg/day dose of r-hGH (Serono formulation) was a gain in height-SDS of between 1.06 and 1.54 SDS. These values compare well with the observed values of 1.04, 1.13, and 1.40 in the non-Serono studies. The simulation exercise resulted in a point estimate of 1.2 for the mean gain in height-SDS for the Serono-sponsored studies (Table 4). The difference in estimate between the Serono-sponsored studies and the non-Serono studies was 0.05 SDS. The lower 95% confidence limit for the difference between Serono-sponsored and non-Serono studies was –0.15 SDS. This indicates that it is highly unlikely that the outcome for height-SDS from the Serono studies with a r-hGH dose of 0.033 mg/kg/day would have been more than 0.15 SDS inferior to that observed in the non-Serono studies. Considering that the estimate for gain in height-SDS in the non-Serono studies was 1.16 SDS, one can safely assume that the gain in height-SDS with the Serono r-hGH formulation after a 2-yr treatment with a 0.033 mg/kg/day dose would be in the same range, a result which can be considered a meaningful therapeutic response.

Table 2 - *Results of the covariance regression analysis.*

Parameter	Estimate	SE	t-value[a]	PR > t[b]
Intercept	–1.49	0.67	–2.21	0.0488
Dose (β1)	44.02	11.15	3.95	0.0023
(Dose)^2 (β2)	–305.59	142.97	–2.14	0.0558
Baseline height-SDS	–0.48	0.19	–2.48	0.0305

[a] t-value: Student's t-value calculated according to the t-distribution function and the corresponding number of degrees of freedom in the model; [b] PR > t: the observed probability is > the Student's t-value. SDS: SD score. SE: standard error.

DISCUSSION

The results from this meta-analysis confirm the previous findings from individual studies that treatment with r-hGH of short children born SGA is associat-

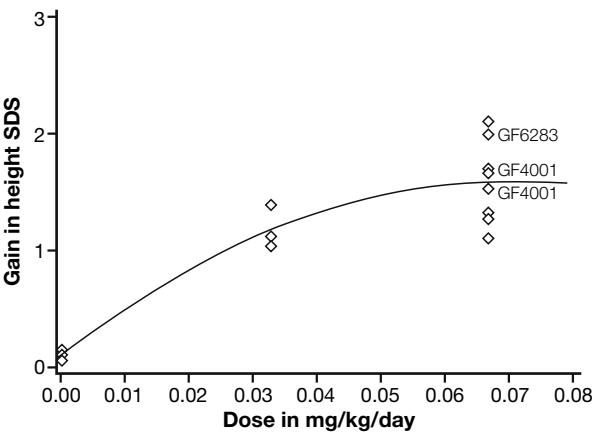

Fig. 1 - *Quadratic regression adjusted by height SD score (SDS) at baseline of the gain in height-SDS by dose after 2-yr treatment with recombinant human GH.*

Table 3 - *Estimated change in height-SD score (SDS) after 2-yr treatment with 0.033 mg/kg/day recombinant human-GH.*

Study number (see Table 1)	6283	4001 [T]	4001 [C]
Observed change in height-SDS at 0.067 mg/kg/day	2.00	1.68	1.52
Estimated change in height-SDS at 0.033 mg/kg/day	1.54	1.22	1.06

[T] and [C] are 2 treatment groups within the same study.

Table 4 - *Results from the simulation of the mean estimate of change in height-SD score (H-SDS) for treatment with 0.033 mg/kg/day of r-hGH (Serono formulation).*

Quadratic transformation adjusted for baseline H-SDS	
Number of simulations, no.	500
Mean H-SDS estimate of translated study data at 0.033 mg/kg/day	1.22
Mean H-SDS of observed study data at 0.033 mg/kg/day	1.16
Mean difference between observed and estimated H-SDS data	0.054
Lower limit of two-sided 95% CI of the mean H-SDS difference	–0.15

CI: confidence interval.

ed with a dose-response effect. Treatment of children for 2 yr with r-hGH, 0.067 mg/kg/day, results in a greater gain in height-SDS compared with the same duration of treatment using half this dose.
The difference in effect size between the 2 active doses can be quantified as approximately 0.48 SDS. Therefore, the difference between the 2 doses is consistent, significant, and can be modeled into a reliable quadratic equation that provides a good fit to the experimental data.
A trial simulation with a proc.mixed model, demonstrated that the mathematical model was able to provide a reliable estimate of efficacy for the lower dose of Serono r-hGH formulation not yet studied in clinical trials. The estimated mean gain in height-SDS after 2-yr treatment was found to closely match that observed experimentally with other formulations of r-hGH. The calculated difference of less than 5 mm in actual height was not clinically significant.
The statistical probability that the gain in height-SDS with Serono r-hGH fomulation would be greater than 0.15 SDS points less than that observed with other formulations with the 0.033 mg/kg/day dose was demonstrated to be very low. Therefore, 2-yr treatment with 0.033 mg/kg/day of Serono r-hGH formulation would result in a clinically relevant increase in height-SDS of 1.19 (0.18).

From this analysis it can be concluded that for the majority of short children born SGA, treatment with 0.033 mg/kg/day of any formulation of r-hGH tested in clinical trials or assessed in this study should provide a meaningful therapeutic response. GH dose has been shown to be the most important predictor of growth response during the 1st yr of treatment. During the 2nd yr of treatment, age at the time of treatment onset was the most important predictor of growth response (with a smaller response in older children) and GH dose was the second most important factor (13).
This meta-analysis does not contain information about IGF-I levels, whose supraphysiological levels may have adverse effects in the long term, or data on poor responder subjects, or on possible rapid bone age progression in some subjects showing a tendency to precocious puberty. This reflects the limitations of a meta-analysis. For instance, there is little information on IGF-I levels in the published literature, little agreement on "normal" values and, since different IGF-I assays may have been used in the different studies, it would be inappropriate to compare IGF-I levels between such studies. Another limitation of this meta-analysis is that it is based on data published up to March 2004 and so does not contain data from more recent publications. A review of the literature from 2005-2007, using the same search terms as before, identified 7 papers that might potentially affect the conclusions of this meta-analysis (19-25) and these were reviewed in detail. Of the 7 papers, 3 can be excluded because the treatment duration is shorter than that of the studies in this meta-analysis (19, 20, 22). The height-SDS data from the remaining 4 studies (21, 23-25) fall within the range of the data included in the 2004 meta-analysis and, therefore, would not significantly change the analysis results.
This study confirms that there is a clear dose-response relationship for r-hGH when used for the treatment of short children born SGA, with the higher dose of r-hGH resulting in a greater gain in height-SDS over 2 yr. Some children may benefit from the greater gain in height that is achievable with the higher dose of r-hGH over a relatively short treatment period.

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