Relationship between the Dose of Recombinant Human Growth Hormone (rhGH) and Insulin Growth Factor-1 (IGF-1) in Adult Patients with Growth Hormone Deficiency (AGHD)

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Objectives

The dosing requirements and clinical effectiveness of rhGH have been extensively studied in AGHD patients. It has become well known that the growth-promoting and metabolic actions of rhGH are mediated principally through the synthesis of Insulin Growth Factor-I (IGF-I) [1]. In fact, treatment in patients is often guided by the IGF-I normal range achieved after rhGH administration. The purpose of this meta-analysis was to characterise the relationship between rhGH dose, time, patient characteristics and IGF-1 in AGHD patients.

Methods

Database: All uncontrolled and controlled trials that reported a change from baseline in IGF-1 in AGHD patients with at least one week of rhGH treatment were included in the database. The database contains 118 trials with 225 unique treatment arms representing 4298 patients and main patients' characteristics were collected (Table 1). Three trials with patient level data were included to obtain more information on the relationship between covariates and IGF-1 response.

Table 1. Covariates overview of IGF-1 database

Covariate	Median (range)
Dose (ug/kg/day)	10 (1 to 50)
Age (year)	43.6 (18.6 to 69)
Weight (kg)	77.9 (45.9 to 96.8)
% male	61.1 (0 to 100)
Baseline IGF-1 (ng/ml)	87 (8 to 223)
Dose adjustment (fixed/titration/withdraw) (no. of patients)	2190/2061/47

Modelling: A nonlinear mixed effect regression method (function NLME in Splus)) was utilized to analyse dose response data for IGF-1 and maximum likelihood estimates of the model parameters was calculated. A log transformation was used to normalize the variance across the response range. The variance ($\sigma 2/Nik$) of residual variability is weighted by sample size (Nik) in each arm of the trial. A compound symmetry correlation structure was assumed between the IGF-1 observations within one arm of a trial to account for the repeated measurements over time and was defined for the εij within a specific treatment arm. The correlation (ρ) was estimated.

The model structure is expressed as:

$$t\{Y_{ijk}\} = t\{base_{ik} + E_0 + E_{drug}\} + \eta_i + \varepsilon_{ijk} \qquad \text{Eq. 1}$$

t{x}: log-transformation
Yijk: observed response at week j in the kth arm of the ith trial
Baseik: observed baseline.
E0: placebo effect
Edrug=Emax*doseijk/(doseijk+ED50) :dose response relationship
ηi: between trial variability
εijk: residual variability

The final covariate model for ED50 is shown below:

$$\log(ED_{50}) = ED_{50,0} + ED_{50,1}\cdot(baseIGF - 80) + ED_{50,2}\cdot(male) + ED_{50,3}\cdot\log(weight/75) +$$
$$ED_{50,4}\cdot(intervention = HRT) + ED_{50,5}\cdot(doseadjust = titration) \qquad \text{Eq. 2}$$

Results

The dose response data for IGF-1 was well described by an Emax model (Figure A). The parameters were well estimated (Table 2). The ED50 was found to be significantly dependent on baseline IGF-1, gender, body weight, and dose titration (Eq.2). Gender was the most significant one (Figure B). Female subjects were less sensitive to treatment needing a 1.7-fold higher dose to get a certain IGF-1 response than males (typical male ED50=9.5μg/kg/day vs. female 16.5 μg/kg/day). Weight is not a significant covariate in the model that is based on total dose. This suggests that body weight adjusted dosing might be not necessary.

The dose required to normalize IGF-1 to 180 ng/ml (the mid-point of the normal range for 35 years old AGHD patients) with different baseline iGF-1 is shown in Figure C. The dose required is 0.23 [0.21 to 0.27] mg/day in a typical male with adult onset GHD and 0.40 [0.35 to 0.45] mg/day in a typical female with baseline IGF-1 of 90 ng/ml.

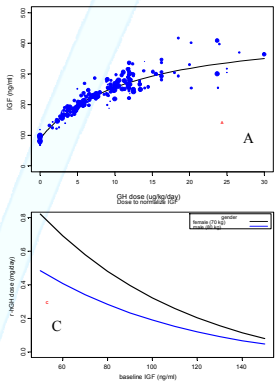

Figure A: Observed and predicted IGF-1 dose response relationship.

Figure B: Impact of gender on the IGF-1 dose response relationship

Figure C: Dose required to normalize IGF-1 to 180 ng/ml

Table 2. Maximum likelihood model parameter (main) estimates for the final IGF-1 dose response model with 90% CI.

Parameter	Estimate [90% CI]
E_{max} (ng/mL)	365 [315 to 414]
ED_{50} (ug/kg/day)	2.81 [2.56 to 3.06]
ED_{50} (male)	-0.484 [-0.635 to -0.333]
ω (inter-trial variability)	0.138 [0.118 to 0.161]
ρ (correlation)	0.569 [0.52 to 0.615]
σ (residual error)	0.535 [0.504 to0.568]

Discussion and conclusions

This meta-analysis provided a broad overview and understanding of the IGF-1 dose response relationship and the impact of key covariates. Gender is the most important factor to impact the response. Females need higher doses to reach the same effect as males. The model can be used to predict the IGF-1 response in a variety of patient populations.

Reference:
[1]. A Rees, M Scanlon. Growth Hormone Deficiency in Adults – 10 Years of KIMS. P15, 2004