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Monitoring of growth hormone treatment by the electronic auto-injection device easypod™ allows to improve the outcome and maximize adherence in patients with generally high adherence rates

KKP Hartmann[1] and the SAIZEN-EDC Study Group (Germany)

[1]Medical Centre for Childhood and Adolescence in Paediatric Endocrinology and Diabetology, Frankfurt, Germany

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Background

- Patients with growth hormone (GH) deficiency (GHD) and those born small for gestational age (SGA) require long-term supplementation with GH.
  - Saizen® (somatropin, Merck Serono, Darmstadt, Germany*) is a recombinant human GH (r-hGH) approved in many countries worldwide for these indications.†
- To achieve an optimal growth response during therapy with r-hGH, it is important that patients adhere to the prescribed GH dose.[1–3]
- The easypod™ electronic auto-injector (Merck Serono S.A., Switzerland†) enables an accurate recording of the r-hGH dose administered and adherence.[4]
- High adherence with the easypod™ device has been reported previously.[5]
  - Overall adherence was generally high (mean [standard deviation (SD)] 91.2 [12.2] %).
  - An adherence rate ⩾85.7% (i.e. fewer than one missed r-hGH dose per week) was reported for 78.7% of patients treated with r-hGH.
  - Pre-pubertal patients had higher mean (SD) adherence rates than pubertal patients (96.5 [3.9] versus 89.1 [13.7] %; p<0.005).
- Recently, we reported adherence rates for patients treated with r-hGH using the easypod™ auto-injector from a retrospective, observational study.[6]
  - Here, we report additional analyses of the data from the same study.

Objective

- To evaluate the impact of adherence to r-hGH therapy, and actual administered r-hGH dose, on clinical outcomes during the first 2 years of treatment in patients with growth disorders.

Methods

Study design and patients

- Retrospective, observational, open-label, non-controlled, multicentre study in patients diagnosed with GHD or born SGA.
- Patients attending 11 paediatric endocrinology centres in Germany from October 2009 to May 2013 were included in this study.
- Patients received treatment with r-hGH administered using easypod™ at individualised doses of 0.025–0.035 mg/kg/day.

Data collection

- The actual r-hGH dose received by each patient, and the injection time, were measured automatically by the easypod™ device.
- Adherence data were collected using the easypod™ device in conjunction with the clinical kit software.
- easypod™ data were uploaded to the internet-based Saizen® electronic data capture system (SAIZEN-EDC).
- Growth data were obtained from patient records, which were also uploaded to the SAIZEN-EDC.

Analysis of data

- Only descriptive statistical methods were used.
- Growth outcomes analysed were growth velocity (cm/year) and height standard deviation score (SDS).

  Height SDS was calculated as:

$$\text{Height SDS} = \frac{H - \bar{H}}{SD(\bar{H})}$$

  in which H is the height measured at a specific age, $\bar{H}$ is the reference mean height for the corresponding chronological age and $SD(\bar{H})$ is the SD of the reference mean height.
- Data are presented for groups stratified as follows:
  - Adherence rate: patients were split into two groups according to whether their mean adherence rate over 2 years of treatment was 87.5% or greater (high adherence group) or lower than 87.5% (low adherence group).
  - The adherence cutoff of 87.5% was selected as being equivalent to missing one injection per week.
  - Indication: GHD or SGA.
  - Dose range: patients were split into four dose groups ranging from high (quartile 1) to low (quartile 4) dose r-hGH based on the actual r-hGH dose administered (calculated as the prescribed dose multiplied by the adherence rate).

Results

Patients and treatment

- Fifty-three patients (GHD, n=36; SGA, n=17), mean (SD) chronological age at start of GH therapy of 10.7 (3.7) years, had a mean (SD) prescribed r-hGH dose of 0.033 (0.006) mg/kg/day.
- Taking adherence rate into account, the actual mean (SD) r-hGH dose administered was 0.029 (0.005) mg/kg/day.

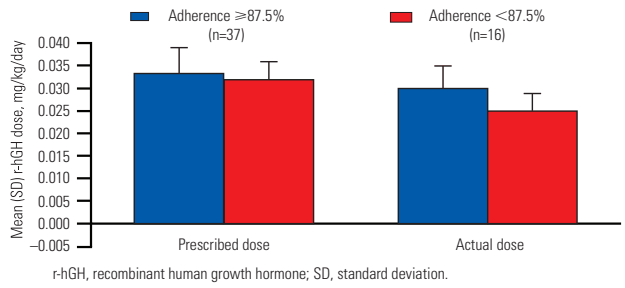
Growth outcomes by adherence rate

- Thirty-seven patients (GHD, n=22; SGA, n=15) with a mean (SD) chronological age of 9.30 (3.46) years at start of GH therapy had a 2-year adherence rate of ⩾87.5% and received a mean (SD) r-hGH dose of 0.030 (0.005) mg/kg/day (**Table 1, Figure 1**).
  - After 2 years of r-hGH treatment, these patients had a mean (SD) growth velocity of 8.02 (1.74) cm/year and an increase in height SDS of 0.98 (0.70) (**Table 1, Figure 2**).
- Sixteen patients (GHD, n=14; SGA, n=2) with a mean (SD) chronological age of 14.21 (1.45) years at start of GH therapy had an adherence rate <87.5%, and received a mean (SD) r-hGH dose of 0.025 (0.004) mg/kg/day (**Table 1, Figure 1**).
  - After 2 years, these patients had a mean (SD) growth velocity of 8.05 (2.23) cm/year with an increase in mean (SD) height SDS of 0.85 (0.65) (**Table 1, Figure 2**).

Table 1. Growth outcomes by high (⩾87.5%) or low (<87.5%) adherence rate.

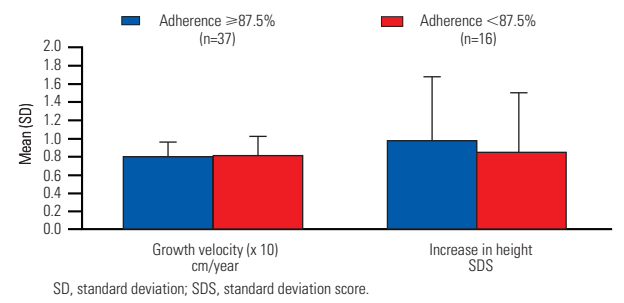
	Patients with adherence ⩾87.5% (n=37)	Patients with adherence <87.5% (n=16)
Mean (SD) age at start of GH therapy, years	9.30 (3.46)	14.21 (1.45)
Mean (SD) adherence, %	94.96 (3.45)	79.22 (6.74)
Mean (SD) prescribed dose of r-hGH, mg/kg/day	0.033 (0.006)	0.032 (0.004)
Mean (SD) actual dose of r-hGH received, mg/kg/day	0.030 (0.005)	0.025 (0.004)
Mean (SD) growth velocity, cm/year	8.02 (1.74)	8.05 (2.23)
Mean (SD) increase in height SDS	0.98 (0.70)	0.85 (0.65)

GH, growth hormone; r-hGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score.



r-hGH, recombinant human growth hormone; SD, standard deviation.

Figure 1. Prescribed and actual doses of r-hGH in patients with high or low adherence.



SD, standard deviation; SDS, standard deviation score.

Figure 2. Comparison of growth outcomes by high and low adherence after 2 years of treatment.

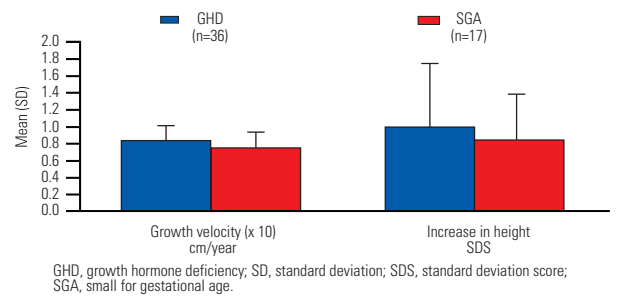
Growth outcomes by indication

- Analysis of growth by indication showed that the group with GHD responded better to r-hGH treatment than the group with SGA, despite lower adherence and older age at start of GH therapy (by almost 3.5 years) (**Table 2, Figure 3**).
  - GHD: mean (SD) growth velocity was 8.32 (1.84) cm/year and mean (SD) height SDS increased by 0.99 (0.74).
  - SGA: mean (SD) growth velocity was 7.41 (1.87) cm/year and mean (SD) height SDS increased by 0.83 (0.55).

Table 2. Growth outcomes by growth disorder.

	Patients with GHD (n=36)	Patients born SGA (n=17)
Mean (SD) age at start of GH therapy, years	11.86 (3.07)	8.38 (3.96)
Mean (SD) adherence, %	88.92 (9.04)	92.94 (7.22)
Mean (SD) prescribed dose of r-hGH, mg/kg/day	0.030 (0.005)	0.035 (0.004)
Mean (SD) actual dose of r-hGH received, mg/kg/day	0.027 (0.005)	0.032 (0.004)
Mean (SD) growth velocity, cm/year	8.32 (1.84)	7.41 (1.87)
Mean (SD) increase in height SDS	0.99 (0.74)	0.83 (0.55)

GH, growth hormone; GHD, growth hormone deficiency; r-hGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age.



GHD, growth hormone deficiency; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age.

Figure 3. Comparison of growth outcomes by indication after 2 years of treatment.

Growth outcomes by r-hGH dose received

- Due to the differences in growth responsiveness observed between the GHD and SGA groups, further analyses included patients with GHD only.
- Differences in growth response between high- and low-dose groups were seen.
  - Patients in the high-dose group (quartile 1: mean [SD] adherence rate 95.04 [3.96] %; actual mean [SD] r-hGH dose 0.033 [0.004] mg/kg/day) had a mean (SD) growth velocity of 8.82 (1.19) cm/year and an increase in mean (SD) height SDS of 1.00 (0.54) (**Table 3**).
  - In contrast, patients in the low-dose group (quartile 4: mean [SD] adherence rate 82.73 [11.72] %; actual mean [SD] r-hGH dose 0.021 [0.003] mg/kg/day) had a mean (SD) growth velocity of 8.29 (2.43) cm/year and an increase in mean (SD) height SDS of only 0.79 (0.66) (**Table 3**).
  - Of note, patients in the high-dose group were younger (by almost 3 years) at start of GH therapy than those in the low-dose group (**Table 3**).

Table 3. Growth outcomes by r-hGH dose quartile.[a]

	Patients in dose quartile 1 (n=9)	Patients in dose quartile 2 (n=9)	Patients in dose quartile 3 (n=9)	Patients in dose quartile 4 (n=9)
Mean (SD) age at start of GH therapy, years	10.47 (3.07)	11.32 (2.61)	11.42 (4.55)	13.40 (1.85)
Mean (SD) adherence, %	95.04 (3.96)	92.40 (6.05)	87.92 (8.55)	82.73 (11.72)
Mean (SD) prescribed dose of r-hGH, mg/kg/day	0.034 (0.005)	0.032 (0.002)	0.030 (0.003)	0.026 (0.004)
Mean (SD) actual dose of r-hGH received, mg/kg/day	0.033 (0.004)	0.028 (0.001)	0.026 (0.005)	0.021 (0.003)
Mean (SD) growth velocity, cm/year	8.82 (1.19)	8.19 (1.38)	7.99 (1.96)	8.29 (2.43)
Mean (SD) increase in height SDS	1.00 (0.54)	0.78 (0.52)	1.37 (1.05)	0.79 (0.66)

[a]Where quartile 1=highest and quartile 4=lowest r-hGH dose.
GH, growth hormone; r-hGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score.

Conclusions

- The easypod™ auto-injector allows GH dose and adherence rate to be accurately recorded.
- Maximising adherence is important to the success of GH treatment in patients with GHD or born SGA.
- In this analysis of easypod™ data, growth responsiveness for patients with better adherence (⩾87.5%) to treatment with r-hGH was compared with patients with worse adherence (<87.5%).
  - Patients in the group with better adherence were younger than those with worse adherence; this is in line with previous results.[6]
  - Height SDS was increased in patients with better adherence compared with those with a lower rate of adherence, although growth velocities were similar.
  - The age range of the study subjects would affect the expected growth response, making growth velocities difficult to interpret.
- Despite lower adherence, patients with GHD had higher growth velocity and increased height SDS compared with patients who were born SGA; patients in the GHD group were also older than those in the SGA group.
- These data confirm the lower responsiveness to r-hGH in SGA compared with GHD that has previously been described.[7,8]
  - As SGA is an indication for GH therapy, such patients are not required to undergo the complete GH secretion diagnostic procedure that is needed for patients with GHD.
  - Furthermore, most patients who are born SGA are smaller than patients with partial GHD, and therefore diagnosed and treated with r-hGH earlier.
- In addition, the effect of r-hGH treatment on patients with GHD was compared in relation to the actual administered r-hGH dose.
  - Patients who received an r-hGH dose within the first quartile of the dose range for all patients (0.033 mg/kg/day) had better growth velocity than those who received a lower dose; these two groups also differed in terms of their age, with those in the low-dose group older than those in the high-dose group.
  - There was an unclear relationship between dose and increase in height SDS, which might be a result of the small sample size in each dose quartile. It is possible that the quartile 3 dose group, which had the greatest increase in height SDS although at a poor dose level, was unduly influenced by the two very young patients with extremely low height SDS at the start of the study (3.7 and 2.3 height SDS gain over the 2 years).
- In this novel study, the use of the easypod™ auto-injector has shown that adherence has an impact on growth outcomes, even at relatively high adherence rates. Physicians should target adherence of ⩾90%, as small decreases even at the higher end of adherence rates make a difference.
- Data suggest that better adherence to r-hGH therapy, as measured and controlled by the easypod™ auto-injector, may result in improvements in growth responsiveness in patients with GHD or SGA.

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