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Adherence and long-term outcomes of growth hormone therapy with easypod™ in pediatric subjects: Spanish ECOS study

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Abstract

Background: Non-adherence to r-hGH treatments occurs in a variable percentage of subjects. One problem found when evaluating adherence is the great variability in methods of detection and definitions utilized in studies. This study assessed the level of adherence in subjects receiving r-hGH with the easypod™ electronic device.

Methods: National, multicenter, prospective and observational study involving 238 subjects (144 with GH deficiency (GHD), and 86 with small for gestational age (SGA), 8 with Turner Syndrome), who received r-hGH with easypod™ for at least 3 months before inclusion. The follow-up period was 4 years.

Results: Overall adherence was 94.5%; 97.5% after 6 months, 95.3% after 1 year, 93.7% after 2, 94.4% after 3 and 95.5% after 4 years of treatment. No differences in adherence were observed between prepubertal and pubertal groups and GHD and SGA groups. Change in height after 1 and 2 years, change in height SDS after 1 and 2 years, HV after 1 year, HV SDS after at 1 and 4 years, change in BMI after 1 year and change in BMI SDS at 1 and 2 years showed significant correlation with adherence. No significant differences in adherence according to IGF-I levels were found in follow-up visits or between groups.

Conclusions: The easypod™ electronic device, apart from being a precise and objective measure of adherence to r-hGH treatment, allows high compliance rates to be achieved over long periods of time. Adherence significantly impacts growth outcomes associated with r-hGH treatment.

Key Words

- ▶ adherence
- ▶ r-hGH
- ▶ easypod
- ▶ electronic device
- ▶ long-term
- ▶ outcomes
- ▶ pediatrics
- ▶ e-health

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Introduction

Since the 60s, GH has been the mainstay of treatment for children with GH deficiency (GHD) (1). With the discovery of recombinant human growth hormone (r-hGH),

the treatment has been extended to other conditions, such as Turner syndrome (TS), chronic renal insufficiency (CRI) and children born small for gestational age (SGA)

(2, 3). Pathologies requiring the administration of r-hGH in pediatric patients show a great variability in severity (especially among secretion pathologies) and in sensitivity to the hormone (4). Treatment with r-hGH has been shown to be effective in children and adolescents with GHD, increasing short-term growth and adult height (5, 6). GH therapy requires daily subcutaneous injections for long periods of time (7). Some studies have suggested that non-adherence to treatment occurs in a variable percentage of subjects (8, 9, 10). The main cause for minor efficacy in r-hGH therapy is the lack of adherence to treatment or non-persistence with the prescription (11). Since dosing has to be adjusted depending on the response to treatment, it is necessary, initially, to ensure adherence to treatment in order to evaluate its response. Non-adherence to the prescribed treatment is directly associated with worse clinical outcomes, increased healthcare costs and may affect the benefit–risk balance of treatments, especially in chronic diseases (12). One of the problems found at the time of evaluating adherence to r-hGH treatments is the great variability in methods of detection and definitions of adherence utilized in studies (8, 9, 10). To provide a precise and objective measure of adherence, electronic devices can be used to monitor and administer treatment. The r-hGH electronic auto-injector device, easypod™ (Merck Serono International S.A.), has been specifically designed to ease the use of these daily injectors and to provide reliability and convenience to users by recording the dosing history and using preprogrammed doses; in other words, to provide an e-health tool to patients (13). Despite this term has evolved in the last decade, e-health is defined by the World Health Organization (WHO) as ‘the use of information and communication technologies for health’ (14). Since easypod™ records the number of doses administered, adherence can be accurately assessed. The multinational easypod™ connect observational study (ECOS) was specifically designed to quantify adherence in subjects receiving r-hGH with easypod™ and to characterize the impact of adherence on clinical outcomes and identify adherence patterns (15). This study aimed to evaluate adherence as a factor involved in the response to treatments with r-hGH. The present manuscript shows results obtained from the Spanish ECOS study (ClinicalTrials.gov identifier: NCT01376921) and the main objective of the study was to assess the level of adherence in subjects receiving r-hGH with the electronic device, easypod™.

Subjects and methods

Patients

This national, multicenter, observational study involved subjects aged between 2 and 18 years old or over 18 years with no fusion of growth plates, who received r-hGH (Saizen®, Merck Serono S.A.) with the easypod™ electronic device for at least 3 months before inclusion into the study. The period of follow-up was up to 5 years; however, due the low number of patients at that time, results are only shown for up to 4 years. Exclusion criteria to participate in the study were previous treatment with r-hGH other than Saizen®; hypersensitivity to the active ingredient or excipients; subjects with fused growth plates; contraindications to r-hGH or participating in another clinical study. Subjects were identified from the investigator’s review of medical charts. Informed consent signed by parents or legal guardians was obtained from all subjects. All procedures were in accordance with the Declaration of Helsinki and approved by the Ethics Committee of each participating center.

Endpoints and variables

The primary endpoint was the adherence to treatment over a follow-up period of 4 years. Adherence data were collected by the means of easypod™ and uploaded at every follow-up visit or at any time point adjacent to the visit if collected remotely, depending on the clinical practice. Adherence was calculated as the percentage of injections received (days) with respect to planned injections. The compliant population was defined as those with $\geq 85\%$ adherence to prescribed treatment (no more than 1 missed dose a week on average) (16). Secondary endpoints included evaluation of the impact of adherence on growth outcomes over the follow-up period; identification of demographic and auxological characteristics of subjects associated with adherence and assessment of the impact of insulin-like growth factor I (IGF-I) levels on adherence over the follow-up period. Demographic, auxological and diagnostic data were obtained from medical charts. All data were collected both retrospectively and prospectively. In contrast with the global ECOS study, demographics, historical information on growth hormone treatment, auxological parameters and adherence were transcribed by investigators onto paper case report forms and not reported electronically. Growth outcomes included height, height standard deviation score (SDS), change in height, change in height SDS, height velocity (HV),

HV SDS, change in HV, change in HV SDS, weight, weight SDS, change in weight, change in weight SDS, BMI, BMI SDS, change in BMI and change in BMI SDS. The SDS variables were calculated by adjusting data with age and gender, according to child growth standards (17). Bone age was measured using the Greulich and Pyle method (18). The IGF-I concentration was classified as high, normal or low according to standard laboratory ranges (established on the heterogeneity of techniques used in the present multicenter study). The proportion of subjects with dose changes was calculated as a percentage of the number of visits with dose changes over the total number of visits.

Determination of sample size and statistical analysis

The ECOS Spain study was planned to be implemented in 50 centers and expected to recruit 300 subjects. Treatment adherence data of 300 subjects would be able to compute the 95% confidence interval (95% CI) around the observed mean percent of adherence with a precision of $\pm 1.7\%$ assuming a standard deviation (s.d.) of 16%. Statistical analysis was performed on the full analysis set (FAS) subpopulation. The FAS subpopulation included subjects with GHD, SGA and TS, according to the new definition established by investigators on June 3, 2016. The FAS subpopulation was also stratified by prepubertal (Tanner stage 1) and pubertal subjects (Tanner stage 2–4). Due to low numbers, subjects with TS were excluded from analyses. Categorical variables were expressed as absolute and relative (%) frequencies; whereas continuous variables as the mean, median, s.d. and 95% CI. Parametric or non-parametric analyses were carried out depending on results of the normality test of each variable. The impact of adherence on growth outcomes at the different follow-up visits was determined by non-parametric Spearman's correlation analysis. The correlation between compliance and growth outcomes, and the impact of adherence on serum IGF-I levels was measured by using a *t*-test or the Wilcoxon–Mann–Whitney test. The identification of demographic and auxological characteristics associated with adherence was performed with a multiple linear regression model. The following predictor variables were considered: age (at inclusion and when starting r-hGH treatment with easypod™), gender, indication (GHD or SGA), person who performed the majority of injections, treatment duration, and height SDS before start of GH treatment. Those variables with a statistical significance ($P > 0.1$) were included in the model.

All statistical procedures were performed using SAS version 9.4. Statistical significance was established when $P \leq 0.05$.

Results

Characteristics of subjects and treatment

A total of 272 subjects consented to participate in the study. Among them, 238 (87.5%) were included in the FAS subpopulation; 212 (89.1%) in the prepubertal and 26 (10.9%) in the pubertal group. The main reason for discontinuation (80.6% of cases) was due to the closure of the study by the sponsor at which point subjects were followed up for at least one year. The FAS subpopulation included 235 (209 prepubertal and 26 pubertal) subjects at 6 months and 1 year after starting the treatment, 176 (160 and 16, respectively) subjects at 2 years, 84 (80 and 4, respectively) subjects at 3 years and 25 (24 and 1, respectively) subjects at 4 years. In the FAS subpopulation, there were no data from three patients regarding if prepubertal or pubertal. In total, 144 subjects presented with GHD, 86 with SGA and 8 with TS. Baseline sociodemographic and clinical characteristics of patients are shown in Table 1. Subjects had a mean age at inclusion of 9.0 ± 3.3 years; approximately half of them were male (51.7%), mainly Caucasian (94.1%). At the time of starting treatment with easypod™, mean height SDS and velocity SDS were -2.6 ± 0.8 and -2.0 ± 1.7 , respectively. No differences in demographic and auxological variables in terms of SDS values were observed between prepubertal ($n=212$) and pubertal ($n=26$) groups. At baseline, 73.1, 23.1 and 3.8% of pubertal subjects had Tanner Stage 2, 3 or 4, respectively. Mean bone age for the prepubertal GHD population ($n=119$) was 6.0 ± 3.1 years, whereas their mean chronological age at inclusion was 9.2 ± 3.1 years. The mean duration of treatment was 26.6 ± 11.6 months (27.2 ± 11.7 months in the prepubertal group, 22.0 ± 8.9 months in the pubertal group, 27.4 ± 11.9 months in the GHD population, and 25.5 ± 10.7 months in the SGA population). Changes in prescribed dose were documented in $61.7 \pm 20.2\%$ of visits over the treatment period; for adjusting it to the recommending dose (mg/kg/day). The main reasons for missed injections were forgetting to inject (78.0%), and holidays, long weekends or not sleeping at home (51.8%). No significant differences were found regarding missed injections and the person who performed the majority of injections.

Table 1 Characteristics of subjects and treatment with easypod™.

	Total (n = 238)	Prepubertal (n = 212)	Pubertal (n = 26)	GHD (n = 144)	SGA (n = 86)
Age					
At inclusion, mean years ± s.d.	9.0 ± 3.3	8.5 ± 3.1	13.4 ± 3.1	9.9 ± 3.4	7.7 ± 2.7
At start of treatment with easypod™, mean years ± s.d.	7.9 ± 3.2	7.3 ± 2.9	12.5 ± 1.8	8.7 ± 3.3	6.6 ± 2.5
Gender, n (%)					
Male	123 (51.7)	112 (52.8)	11 (42.3)	78 (54.2)	45 (52.3)
Female	115 (48.3)	100 (47.2)	15 (57.7)	66 (45.8)	41 (47.7)
Ethnicity, n (%)					
Caucasian	224 (94.1)	199 (93.9)	25 (96.2)	135 (93.8)	81 (94.2)
African	1 (0.4)	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)
Asian	3 (1.3)	3 (1.4)	0 (0.0)	2 (1.4)	1 (1.2)
Other	10 (4.2)	9 (4.8)	1 (3.8)	6 (4.2)	4 (4.7)
Auxological data before starting treatment					
Height SDS, mean (s.d.)	-2.6 (0.8)	-2.6 (0.7)	-2.2 (1.1)	-2.5 (0.8)	-2.6 (0.6)
Weight SDS, mean (s.d.)	-1.3 (0.9)	-1.3 (0.9)	0.9	-1.1 (1.0)	-1.5 (0.8)
HV SDS, mean (s.d.)	-2.0 (1.7)	-2.0 (1.6)	-2.3 (2.3)	-2.4 (1.7)	-1.5 (1.5)
BMI SDS	0.2 (1.4)	0.2 (1.4)	0.3 (1.3)	0.3 (1.5)	-0.2 (1.1)
Bone age, years (s.d.)	6.0 (3.3)	5.4 (2.9)	11.0 (1.3)	6.7 (3.4)	4.8 (2.7)
Treatment with r-hGH					
Prescribed dose, mean mg/kg/day (s.d.)	0.032 (0.005)	0.032 (0.005)	0.033 (0.006)	0.030 (0.004)	0.035 (0.004)
Percentage of reported changes in the prescribed doses over the treatment period, mean % ± s.d.	61.7 ± 20.2	62.0 ± 20.5	58.8 ± 18.1	59.1 ± 22.4	66.1 ± 15.6
Duration of treatment period, mean months (s.d.)	26.6 (11.6)	27.2 (11.7)	22.0 (8.9)	27.4 (11.9)	25.5 (10.7)
Person who performed majority of injections, n (%)					
Parents/legal guardian	161 (67.6)	154 (72.6)	7 (26.9)	85 (59.0)	70 (81.4)
Under parent supervision	54 (22.7)	42 (19.8)	12 (46.2)	40 (27.8)	12 (14.0)
Self-injections	17 (7.1)	11 (5.2)	6 (23.1)	14 (9.7)	3 (3.5)
Not available	6 (2.5)	5 (2.4)	1 (3.8)	5 (3.5)	1 (1.2)
Missed some injection over the treatment period, n (%)	195 (81.9)	173 (81.6)	22 (84.6)	115 (79.9)	73 (84.9)
Reasons for missing injections, n (%)					
Forgot injection	152 (78.0)	137 (79.2)	15 (68.2)	90 (78.3)	55 (75.3)
Holidays/long weekend/not sleeping at home	101 (51.8)	90 (52.0)	11 (50.0)	57 (49.6)	42 (57.5)
Medical reasons	6 (3.1)	5 (2.9)	1 (4.6)	4 (3.5)	2 (2.7)
Tired of injections	7 (3.6)	5 (2.9)	2 (9.1)	4 (3.5)	3 (4.1)
Technical problems with easypod™	14 (7.2)	11 (6.4)	3 (13.6)	6 (5.2)	8 (11.0)
Forgot drug/Easypod™	15 (7.7)	12 (6.9)	3 (13.6)	10 (8.7)	5 (6.9)
Ran out of needle/cartridge	7 (3.6)	7 (4.1)	0 (0.0)	3 (2.6)	4 (5.5)
Others	20 (10.3)	18 (10.4)	2 (9.1)	11 (9.6)	7 (9.6)

BMI, body mass index; GHD, growth hormone deficiency; HV, height velocity; s.d., standard deviation; SDS, standard deviation score; SGA, small for gestational age.

Adherence rates

Mean overall adherence to the treatment was 94.5% (95% CI 92.7–96.3%; [Table 2](#)). Adherence was higher than 90% in all follow-up visits, that is 97.5% (95% CI 96.5–98.5%, $n=234$) after 6 months, 95.3% (95% CI 93.3–97.2%, $n=232$) after 1 year, 93.7% (95% CI 91.1–96.2%, $n=174$) after 2 years, 94.4% (95% CI 91.5–97.3%, $n=84$) after 3 years and 95.5% (95% CI 92.7–98.3%, $n=25$) after 4 years of starting treatment with easypod™. Adherence for prepubertal and pubertal

groups was 94.4% (95% CI 92.4–96.4%) and 95.5% (95% CI 92.8–98.1%), respectively. In the case of the GHD and SGA populations, adherence was 95.2% (95% CI 93.3–97.0%) and 93.0% (95% CI 89.1–96.9%). No differences in adherence were observed between the prepubertal and pubertal groups or the GHD and SGA populations. Adherence to treatment among the compliant population ($\geq 85\%$ adherence) was 97.5% after 6 months, 93.2% after 1 year, 92.1% after 2 years, 91.7% after 3 years and 92.0% after 4 years of starting treatment with easypod™ ([Fig. 1](#)).

Table 2 Adherence to the treatment through different follow-up visits.

	Overall		6 months		1 year		2 years		3 years		4 years	
	n available	Mean (95% CI)	n available	Mean (95% CI)	n available	Mean (95% CI)	n available	Mean (95% CI)	n available	Mean (95% CI)	n available	Mean (95% CI)
Total	236	94.5% (92.7-96.3)	234	97.5% (96.5-98.5%)	232	95.3% (93.3-97.2%)	174	93.7% (91.1-96.2%)	84	94.4% (91.5-97.3%)	25	95.5% (92.7-98.3%)
Prepubertal	210	94.4% (92.4-96.4)	208	97.7% (96.6-98.7%)	207	95.1% (93.0-97.3%)	158	93.6% (90.8-96.4%)	80	94.3% (91.3-97.3%)	24	95.6% (92.7-98.5%)
Pubertal	26	95.5% (92.8-98.1)	26	96.2% (93.4-99.1%)	25	96.6% (94.1-99.2%)	16	94.7% (90.4-98.9%)	4	97.1% (94.4-99.8%)	1	93.6%
GHD population	142	95.2% (93.3-97.0)	141	97.0% (95.5-98.6)	142	93.9% (90.8-97.0)	106	93.8% (90.4-97.1)	55	95.2% (92.6-97.8)	17	95.9% (92.5-99.2)
SGA population	86	93.0% (89.1-96.9)	85	98.1% (97.5-98.7)	83	97.4% (96.1-98.7)	63	93.1% (88.7-97.5)	26	92.3% (84.5-100.1)	7	94.4% (87.0-101.9)

95% CI, 95% confidence interval; GHD, growth hormone deficiency; SGA, small for gestational age.

IGF-I levels and adherence

The IGF-I values were below the laboratory range at baseline in 29.0% of subjects. Among these subjects, 76.6% showed IGF-I values within/above laboratory range after 6 months, 91.7% after 1 year, 93.0% at 2 years, 100% after 3 years and 75.0% after 4 years of starting treatment (Table 3). No significant differences in adherence rate according to IGF-I levels were found in any of the follow-up visits or between prepubertal and pubertal groups or GHD and SGA populations.

Impact of adherence on growth outcomes

Overall change in height after 1 and 2 years (Spearman's correlation=0.170 and 0.217; $P=0.010$ and 0.04 , respectively), change in height SDS after 1 and 2 years (correlation=0.161 and 0.160; $P=0.015$ and 0.035 , respectively), HV after 1 year (correlation=0.206; $P=0.002$), HV SDS after at 1 and 4 years (correlation=0.168 and -0.473 ; $P=0.011$ and 0.041 , respectively), change in BMI after 1 year (correlation= -0.193 ; $P=0.003$) and change in BMI SDS at 1 and 2 years (correlation= -0.238 and -0.171 ; $P=0.002$ and 0.051) showed significant correlation with adherence (Table 4). Regarding the GHD population, change in height after 2 years (Spearman's correlation=0.203; $P=0.037$), height SDS after 1 year (correlation=0.169; $P=0.046$), HV after 1 year (correlation=0.224; $P=0.008$), change in BMI after 2 years (correlation= -0.193 ; $P=0.047$) and change in BMI SDS after 2 years (correlation= -0.214 ; $P=0.047$) showed a significant correlation with adherence. In the case of the SGA population, only change in BMI after 1 year (correlation= -0.246 ; $P=0.025$) and change in BMI SDS after 1 year (correlation= -0.2350 ; $P=0.016$) showed a significant correlation with adherence. The remaining growth outcomes showed no differences between the compliant and non-compliant populations. In the compliant GHD population, the following outcomes were higher than in non-compliant GHD population: height SDS after 2 years (-1.5 ± 0.8 vs -2.0 ± 0.6 , $P=0.047$), HV after 2 years (7.6 ± 1.6 cm/year vs 6.0 ± 1.5 cm/year, $P=0.013$), weight after 3 years (35.8 ± 13.1 kg vs 24.5 ± 10.8 kg, $P=0.025$) and change in weight after 3 years (13.0 ± 5.7 kg vs 8.4 ± 2.1 kg, $P=0.048$). In the SGA population, change in weight after 2 years was significantly higher in the compliant subpopulation (7.1 ± 3.0 kg) than the non-compliant subpopulation (4.5 ± 0.3 kg, $P=0.017$).

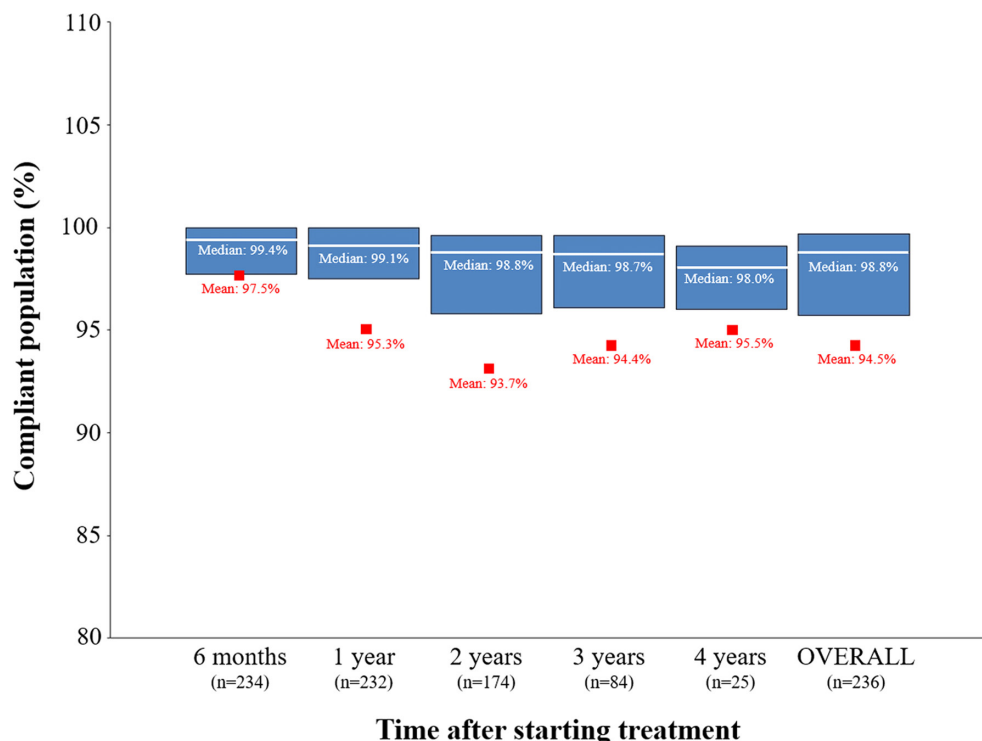


Figure 1

Percentage of compliant population through 4 years of treatment. Blue boxes represent the limits between the 25 and 75% confidence interval. Median and mean values are shown as white lines and red squares, respectively.

Table 3 Baseline IGF-I and percentage of adherence regarding IGF-I levels after starting treatment with easypod™ (IGF-I levels were not associated with percentage of adherence).

	IGF-I laboratory range	Number of patients regarding IGF-I (%)				
		Total	Prepubertal	Pubertal	GHD	SGA
Baseline IGF-I	Above	3 (1.3)	2 (0.9)	1 (3.9)	1 (0.7)	1 (1.2)
	Within	144 (60.5)	127 (59.9)	17 (65.4)	75 (52.1)	62 (72.1)
	Below	69 (29.0)	64 (30.2)	5 (19.2)	55 (38.2)	14 (16.3)
		Adherence, mean % (s.d.)				
		Total	Prepubertal	Pubertal	GHD	SGA
After 6 months	Above	98.2 ± 2.3	98.6 ± 2.2	96.6 ± 2.1	97.7 ± 2.4	100.0
	Within	97.0 ± 10.0	97.4 ± 10.1	93.6 ± 9.3	96.2 ± 13.0	98.0 ± 2.9
	Below	98.3 ± 2.6	98.0 ± 2.7	100.0	98.0 ± 2.7	100.0
After 1 year	Above	97.6 ± 4.4	97.6 ± 4.8	97.7 ± 2.3	97.5 ± 5.2	97.7 ± 3.2
	Within	96.5 ± 11.9	96.3 ± 12.5	97.9 ± 2.6	95.8 ± 14.6	97.3 ± 6.4
	Below	92.2 ± 15.4	92.2 ± 15.4	N.A.	92.2 ± 15.4	N.A.
After 2 years	Above	91.0 ± 24.1	90.9 ± 25.3	91.4 ± 15.7	91.4 ± 24.4	89.2 ± 26.5
	Within	95.4 ± 11.4	95.3 ± 11.9	96.4 ± 3.4	95.0 ± 13.6	95.9 ± 6.8
	Below	87.1 ± 12.1	87.1 ± 12.1	N.A.	87.1 ± 12.1	N.A.
After 3 years	Above	98.2 ± 1.9	98.2 ± 1.9	N.A.	98.2 ± 2.4	98.3 ± 1.6
	Within	93.6 ± 15.7	93.4 ± 16.1	96.8 ± 2.0	95.7 ± 9.3	87.9 ± 25.7
	Below	N.A.	N.A.	N.A.	N.A.	N.A.
After 4 years	Above	96.0 ± 3.5	96.0 ± 3.5	N.A.	96.0 ± 3.5	96.2 ± 5.1
	Within	98.2 ± 1.6	98.2 ± 1.6	N.A.	99.2 ± 0.7	97.9 ± 1.8
	Below	96.4	96.4	N.A.	96.4	N.A.

GHD, growth hormone deficiency; IGF-I, insulin-like growth factor I; N.A., not available (n = 0); s.d., standard deviation; SGA, small for gestational age.

Table 4 Significant impact of adherence on growth outcomes at different follow-up visits, groups and populations.

	Spearman's correlation (<i>P</i> value)				
	Total	Prepubertal	Pubertal	GHD	SGA
Change in height after 1 year	0.170 (0.010) ^a	0.162 (0.021) ^a	0.250 (0.229)	0.147 (0.084)	0.176 (0.111)
2 years	0.217 (0.004) ^a	0.216 (0.007) ^a	0.281 (0.292)	0.203 (0.037) ^a	0.242 (0.056)
Change in height SDS after 1 year	0.161 (0.015) ^a	0.157 (0.025) ^a	0.171 (0.414)	0.144 (0.089)	0.173 (0.117)
2 years	0.160 (0.035) ^a	0.119 (0.137)	0.611 (0.012) ^a	0.146 (0.136)	0.227 (0.073)
Height SDS after 1 year	0.092 (0.164)	0.092 (0.189)	0.144 (0.493)	0.169 (0.046) ^a	-0.075 (0.499)
HV after 1 year	0.206 (0.002) ^a	0.186 (0.008) ^a	0.349 (0.084)	0.224 (0.008) ^a	0.114 (0.304)
HV SDS after 1 year	0.168 (0.011) ^a	0.193 (0.006) ^a	-0.065 (0.759)	0.154 (0.070)	0.152 (0.171)
4 years	-0.473 (0.041) ^a	-0.473 (0.041) ^a	N.A.	-0.283 (0.348)	-0.943 (0.005) ^a
Change in BMI after 1 year	-0.193 (0.003) ^a	-0.162 (0.020) ^a	-0.364 (0.074)	-0.150 (0.077)	-0.246 (0.025) ^a
2 years	-0.126 (0.099)	-0.069 (0.389)	-0.609 (0.012) ^a	-0.193 (0.047) ^a	-0.064 (0.619)
Change in BMI SDS after 1 year	-0.238 (0.002) ^a	-0.214 (0.011) ^a	-0.327 (0.111)	-0.181 (0.055)	-0.350 (0.016) ^a
2 years	-0.171 (0.051) ^a	-0.137 (0.146)	-0.636 (0.008) ^a	-0.214 (0.047) ^a	-0.214 (0.185)

^aSignificant correlation.

BMI, body mass index; GHD, growth hormone deficiency; HV, height velocity; N.A., not available (*n* = 0); SDS, standard deviation score; SGA, small for gestational age.

Subject's characteristics associated with adherence

In the univariate analysis, age at inclusion and at start of treatment, duration of treatment and height SDS before starting treatment showed a *P* value of 0.10 and were therefore included in the multivariate analysis. This multiple linear regression model did not show significant differences on treatment adherence (data not shown). In the GHD population, female subjects (96.4%) showed a significant higher adherence than male subjects (94.2%, *P* = 0.037). Results of the multiple linear regression model in the GHD and SGA populations did not show significant differences on treatment adherence when adjusted for other factors such as age at inclusion and at start of treatment, duration of treatment and height SDS in the FAS subpopulation or the prepubertal and pubertal groups.

Discussion

Non-adherence is an important problem in chronic pathologies for national healthcare systems as it interferes with the effectiveness of treatments, leading to poor clinical outcomes and increased healthcare costs (10, 19, 20). A parent or guardian is required to perform the injections for pediatrics, and children and adolescents are usually reticent to receive them (19). Treatment devices are frequently used to address this issue, especially by favoring self-injection (such as the electronic ones). The prevalence of non-adherence has been reported to range from 5 to 82% (9), with overall values between 36 and 49% (8). A Spanish study involving 158 children

(121 with GHD and 37 with SGA) receiving r-hGH showed that 33.5% presented a moderate-to-poor adherence (defined by authors as <92% adherence) (10). Adherence, measured according to issued r-hGH prescriptions, was indeed significantly correlated with HV and IGF-I levels. Despite these results, only electronic devices can provide a precise and objective measure of adherence (13, 15). To our knowledge, there are scarce studies specifically designed to measure adherence by using the electronic device, easypod™ (21, 22, 23, 24, 25, 26). Recently, the ECOS study (global, i.e. using overall data of 1190 children from 24 national ECOS studies) has evidenced a median overall rate of adherence of 93.7% (26). An international, multicenter, observational study that evaluated 824 children who received r-hGH as part of their normal care for 3 months, reported a rate of adherence (>92% of injections prescribed) of 87.5% using easypod™ (21). Interestingly, children also completed a questionnaire-based survey to measure adherence and the adherence rate was shown to be 90.2%. A retrospective multicenter study from Spain with 504 r-hGH-naïve children with growth disorders receiving r-hGH with easypod™ (in 81.5% of cases) showed that only 7.4% of children were not completely adherent (24). Adherence rates from our study (overall 94.5%) were as high as described in literature using easypod™, and maintained over 4 years of follow-up; however, rates were higher than previously reported in questionnaire-based retrospective studies (9, 16, 21). Furthermore, adherence rates were higher than those in studies using auto-injector devices in diseases such as diabetes and multiple sclerosis (ranging between 60 and 88%) (27, 28, 29). Studies using needle-free auto-injectors with r-hGH in children (such as Zoma-Jet) have reported

adherence rates from 58% (30) to 97% (31). In our study, no significant differences in adherence to treatment were found between the prepubertal and pubertal groups or the GHD (95.2%) and SGA (93.0%) populations. This result is in concordance with ECOS study (global), which showed median adherences of 93.4 and 95.0%, respectively (26). The use of easypod™ might induce Hawthorne effect on patients. It would also be interesting to evaluate the Hawthorne effect in patients receiving r-hGH with easypod™. The Hawthorne effect refers to the change in the behavior of some individuals participating in clinical trials, feeling that they are being monitored and resulting in better adherence rates and results (32). According to some authors (33), levels of IGF-I are not good indicators for adherence because influenced by factors (such as weight, etiology of GHD or nutrition). This statement is supported by no correlation between levels of IGF-I and adherence found in our study. Furthermore, IGF-I levels only would demonstrate adherence of the treatment just one the previous week to the analysis (34).

On the other hand, in our study, change in height and height SDS, HV and HV SDS showed significant, although weak, correlations with adherence. These results are in concordance with literature and highlight the importance of adherence on clinical outcomes of the treatment (16, 21). In ECOS study (global), adherence showed a significant positive correlation with change in height, change in height SDS, HV and HV SDS; all of them after 1 year (26). It is interesting to note that change, in our study, height SDS after 3 years of treatment was higher in patients with >85% adherence. Given the weak correlations between adherence rate and growth parameters found in our study, conclusions (clinical implications) should be carefully considered.

Finally, some patient factors, such as age and gender, have been shown to influence the response to GH therapies (35). In our study, we failed to identify demographic and auxological characteristics in subjects associated with adherence and growth outcomes over 4-year follow-up. Nevertheless, our predictive variables, including age at inclusion, age when starting r-hGH treatment with easypod™, gender, indication, person who performed injections, treatment duration and height SDS before start of GH treatment, were consistent with those selected in prediction models for long-term growth responses (36). Besides this, in the GHD population, female subjects showed a higher adherence rate than males.

One limitation of the present study was its observational nature as it was not specifically designed (primary objective) to determine the impact of adherence

to the treatment on clinical outcomes. The number of patients with low adherence rates (non-compliant population) was very low, which made it impossible to implement such an analysis. Another limitation was the lack of a control group for comparison purposes. A control group would improve the methodological design of the study and would inform whether or not easypod™ increases the adherence or increases the possibility to monitor the adherence. Nevertheless, in our opinion, comparing our results with data from other published studies was also a pertinent option. Moreover, our results are in concordance with literature, such as ECOS study (global) (26). Further studies, specifically designed to evaluate clinical implications of adherence to r-hGH that involve long periods of time (for example, beyond the fourth year of treatment to evaluate long-term adherence) are thus required. The goal of the present study was to evaluate prospectively the adherence to r-hGH treatment, accurately with easypod™, and identify the associations with growth outcomes and biomarkers, such as IGF-I, for an extended period of time.

Conclusions

Subjects receiving r-hGH with the electronic device easypod™ showed and maintained high adherence to the treatment through 4 years of follow-up, in both prepubertal and pubertal subjects, and in both GHD and SGA populations. Adherence significantly impacts growth outcomes of r-hGH treatment. Knowing accurately the adherence to treatment allows clinicians to establish the best approach and adequate dose-adjustment for patients with GHD. Electronic devices, such as easypod™, are the only tools to determine with precision the adherence to treatments with r-hGH. Moreover, they provide this information without the patient being physically present during the consultation. This emerging field of e-health allows activities to be performed that are aimed to improve adherence to treatments (such as supporting nursing programs or motivational messaging), through the use of digital health tools, the Internet and related technologies.

Declaration of interest

Merck, S.L.U. personnel work in the Medical Department that sponsored the study. The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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