

Adherence and growth outcomes in children with growth disorders: results from the *Easypod*TM Connect Observational Study (ECOS) in Indonesia, Singapore, and Taiwan

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Abstract

Background Non-objective assessments indicate poor patient adherence to growth hormone (GH) prescribed for growth failure, with sub-optimal growth response. The *easypod*TM connect device for GH administration enables real-time, objective assessment of adherence.

Objective To examine adherence with pediatric GH therapy in Asia-Pacific countries and relationship with growth outcomes.

Methods Subjects were children in Indonesia, Singapore, Taiwan enrolled in the multi-national, open-label *Easypod Connect Observational Study (ECOS)*. Adherence during follow-up was the primary endpoint and a relationship with 1-year growth outcomes was assessed by Spearman's product-moment correlations.

Results Over a 1-year time frame, median overall patient adherence was $\geq 89\%$; rates were similar for children with GH deficiency (GHD; $n=17$) and those born small-for-gestational age (SGA; $n=5$), except that median adherence dropped between 9 months (94%) and 1 year (83%) for SGA subjects. Median initial GH dose was $42.3 \mu\text{g/kg/day}$ for GHD subjects and $31.4 \mu\text{g/kg/day}$ for SGA subjects. Median age (12 years) and bone age (13 years) indicated that most children had entered puberty at treatment onset. Clinically meaningful improvements in growth were observed at 1 year in the GHD group, but not the SGA group. Statistically significant correlations between adherence and height change ($P=0.039$) as well as height velocity ($P=0.004$) were observed.

Conclusions Children in Asia-Pacific countries show high adherence over the first year of GH therapy with *easypod*. The *easypod* study also shows that adherence is correlated to good growth outcomes. [Paediatr Indones. 2022;62:79-85; DOI: 10.14238/pi62.1.2022.79-85].

Keywords: *easypod connect*; pediatric GH therapy adherence; growth hormone deficiency; small for gestational age; growth outcomes

Recombinant human growth hormone (GH) is approved for use to promote catch-up growth in children with short stature due to various conditions including growth hormone deficiency (GHD), born SGA without catch-up, and Turner syndrome.¹⁻³ Treatment is aimed to improve linear growth, metabolic parameters, and adult height; outcomes are improved by early start and long treatment duration.⁴⁻⁷ Motivation for long-term commitment to regular injections by patients and/or caregivers may decrease over time as continuous daily subcutaneous injections may be perceived to be burdensome, with less obvious treatment benefits.⁸⁻¹¹ Poor adherence

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to GH therapy is reported to be common, with consequent decrease in efficacy outcomes.¹⁰⁻¹⁴ Thus, non-adherence to the GH injection regimen is a major concern in managing growth disorders.

Regular assessment of adherence and early recognition of non-adherence is essential to identify barriers to optimal management of growth failure. Adherence has generally been assessed at clinic visits, but identifying poor adherence to GH therapy can be difficult, for a variety of reasons.^{8,14} Assessments are frequently subjective, and patients and/or caregivers may not wish to admit to poor adherence, thus overestimating administration rates.^{14,15} Measurements that could be considered objective, such as counting ampules/vials or checking pharmacy records for prescriptions collected, do not confirm that doses have actually been taken.^{14,16}

Techniques that can help overcome barriers to good adherence have been identified,^{14,16} including digital health solutions that have evolved rapidly in recent years. One such digital system is the *easypod*[™] device, designed to improve patient convenience during long-term GH therapy, and currently the only electronic GH injection device available.^{16,17} When using the device, accurate, unbiased data on adherence to treatment is recorded in real-time and includes dates and doses of GH delivered. The *easypod* connect web-based software enters the information into a secure database that can be accessed by healthcare personnel who can then easily and accurately monitor adherence. The multinational *Easypod Connect Observational Study* (ECOS) was conducted to assess treatment adherence among pediatric patients receiving GH via the device.¹⁷ Assessment of correlation between adherence and changes in long-term growth outcomes was included among secondary objectives. The Asia-Pacific countries of Taiwan, Indonesia, and Singapore (ClinicalTrials.gov: NCT02015273) were among those involved in the study. The current report documents the results from these countries.

Methods

The ECOS was an open-label, 5-year longitudinal study conducted in accordance with the principles of the *Good Clinical Practice* (ICH-GCP E6) guidelines and applicable local legal and regulatory requirements.

Written informed consent was obtained from all patients (or their parent/guardian) prior to enrollment. Children recruited to the study had short stature, were aged 2 and 18 years, and had commenced use of the *easypod* device for GH treatment. The study was observational and, thus, all diagnoses and treatment decisions were at the discretion of the investigating physician, according to standard endocrine practice and local regulations. In Taiwan, Indonesia, and Singapore, enrollment commenced in December 2013 and the last patient completed the study in December 2015. All eligible patients had their start date recorded in the case report form, no gaps in injection information for more than 1 week after study entry, and height measurements at baseline and 1 year (± 3 months in each case). Prior exposure to GH, baseline and outcome height determinations, and safety information were recorded by the physicians in the case report forms.

Within the Asia-Pacific countries, 24 children received GH via the *easypod* device (*Saizen*[®], Merck PTE Ltd, Singapore, an affiliate of Merck KGaA, Darmstadt, Germany, *version 5.2*). All 24 patients reported their ethnicity as Asian. One patient, diagnosed as SGA, discontinued at 9 months due to withdrawn consent. One male subject, diagnosed as GHD, completed through reaching near final height at 3 months and was not included in the analyses, therefore, adherence and outcomes analyses were based on 23 patients. Adherence rates, accessed using the *easypod* connect system, were calculated on a cumulative basis as number of days when GH was taken as a percentage of total days, for individual 3-monthly treatment intervals for patients overall and for each indication. Median adherence values as well as 25th and 75th percentiles (Q1 and Q3, respectively) were calculated. Height standard deviation score (SDS) was calculated using the *World Health Organization* reference data¹⁸ and height velocity SDS was calculated using Tanner growth standards.¹⁹ The relationships between adherence rate and clinical outcomes at the end of one year of treatment with *easypod* were analyzed using Spearman's product-moment correlations.

Results

There were 24 children enrolled in the study. Their short stature was due to GHD (18 patients), SGA (5

patients), and Turner syndrome (1 patient). All subjects were already receiving GH prior to study entry. The subjects' demographics and clinical characteristics are summarized in **Table 1**. At baseline, GHD subjects ranged in age from 6 to 16 years, with a mean of 11.6 years, SGA subjects ranged from 3 to 12 years, with a mean age of 8.2 years, and the Turner syndrome subject was aged 15 years. Overall median age was 12 years (Q1=9 and Q3=13 years). Bone age was similar to chronological age, indicating that most subjects had already entered puberty (Tanner stage >1 for 12/19; 63% of patients with data).

The number of patients with available adherence data for each 3-monthly period is shown in **Figure 1**. Data were available for a period of at least 1 year for 10 patients. Overall median adherence rates were ≥89% throughout the 1-year treatment period (**Figure 2**). Median adherence remained ≥89% throughout the year in GHD subjects. In SGA subjects, adherence was >93% up to 9 months, but then decreased to 83% at the 1-year point for patients with data available until then. The single Turner syndrome subject had poor adherence throughout, with 36%, 18%, and 12% at 3, 6, and 9 months, respectively.

The overall median height SDS at baseline was -2.13; the median change at 1 year was 0.34 (**Table**

2). For GHD subjects, the median change in height SDS from baseline to 1 year was 0.34, whereas no gain was seen for SGA subjects, with median change -0.04. Overall median height velocity in the first year of treatment was 6.5 cm/year, with height velocity SDS 1.43, indicating an overall positive growth response. This primarily reflected the positive height velocity SDS in GHD subjects (1.87). The median height velocity SDS remained below normal in the SGA group (-0.74).

The correlations between adherence rate and growth outcomes at 1 year are shown in **Table 2**. Adherence was significantly correlated to absolute change in height in the overall group (0.657; P=0.039), as well as change in height SDS and height velocity (cm/year) for SGA subjects (1.000; P<0.001 for both).

For the patients who had IGF-I SDS determinations at 1 year, the values were within the normal range in 6 of 7 GHD patients and 1 of 2 SGA patients. An IGF-I SDS above normal (>2) was reported for 1 of 7 GHD subjects, 1 of 2 SGA subjects and the 1 Turner syndrome subject. No patients had IGF-I below the normal range at 1 year and no serious adverse events were reported during the study.

Table 1. Baseline subject demographic and treatment data, overall and by cause of short stature

Characteristics	Overall population (n=24)	GHD (n=18)	SGA (n=5)	Turner syndrome (n=1)
Age, years				
Mean (SD)	11.0 (3.0)	11.6 (2.4)	8.2 (3.6)	15 (-)
Range	3-16	6-16	3-12	-
Sex, n (%)				
Female	11	6	4	1
Male	13	12	1	0
Mean bone age*, years (SD)	10.9 (4.0)	11.3 (3.1)	9.0 (8.5)	N/A
Easypod treatment duration, days				
Mean (SD)	374.9 (147.6)	339.2 (127.5)	516.4 (147.8)	274 (-)
Range	99-703	99-570	351-703	-
GH dose at start, µg/kg/day				
Mean (SD)	36.5 (9.0)	37.1 (8.5)	31.5 (9.0)	50.0 (-)
Range	19-50	19-50	19-2	-
Number of dose adjustments, n [§]				
0	12	11	0	1
1	2	1	1	-
2	2	2	0	-
>2	7	3	4	-

*Greulich & Pyle assessment, with available data for 9 GHD and 2 SGA subjects; §One GHD subject reached final height at 3 months and was not included in the analyses; N/A=not available

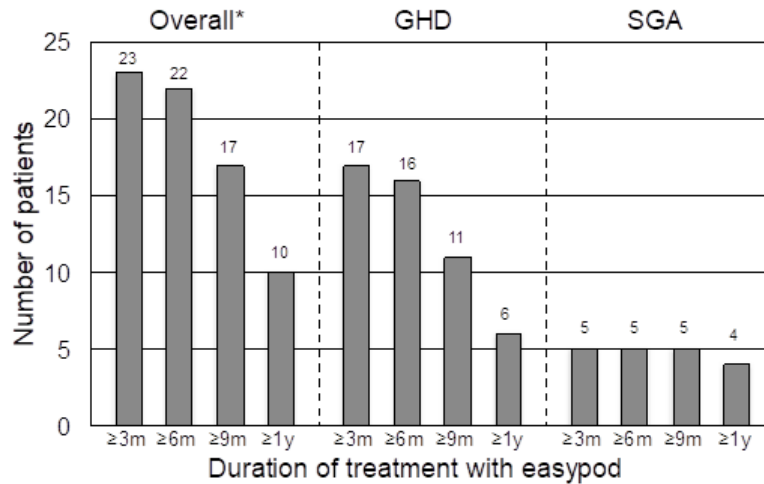


Figure 1. Number of patients with prospective data on adherence to GH treatment via *easypod* over the study period (*including one Turner syndrome patient who received treatment for 9.1 months)

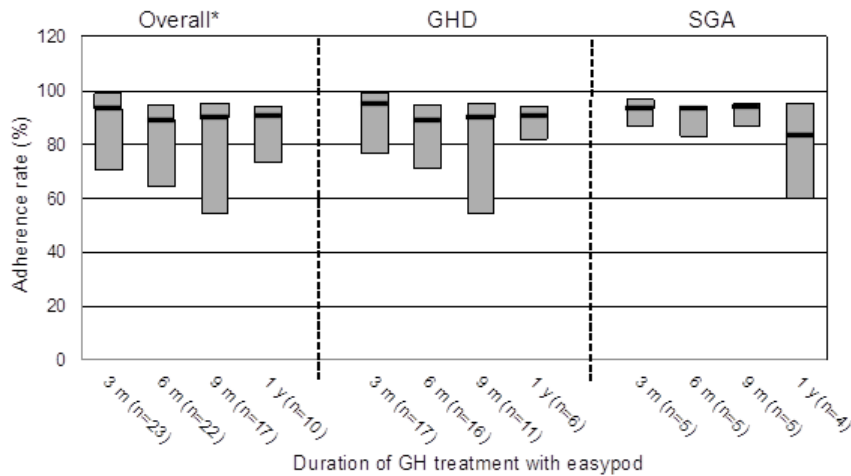


Figure 2. Patient adherence rate to GH treatment via *easypod* by treatment duration for patients overall, GHD, and SGA (*including one Turner syndrome patient who received treatment for 9.1 months). Values are shown as medians, with 25th and 75th percentiles.

Discussion

The multinational study, ECOS, was undertaken to examine GH therapy adherence, determined objectively using *easypod*, and analyze for correlations with growth outcomes in children with growth failure. The Asia-Pacific cohort of ECOS patients had an overall median adherence of at least 89% that was maintained throughout the first year of *easypod* use for GH treatment. This finding was consistent with the adherence rate of 94% for the global ECOS data at 1 year,¹⁷ and adherence rates seen in other short-

term studies of children using the *easypod* device.¹⁹⁻²³ Other studies not using *easypod* reported widely varying adherence rates for GH therapy, from <20% to >90%; however, these studies used non-objective methods of assessment and differing definitions of adherence.^{10,14,24,25} Means of improving adherence, suggested in these reports, included better education and support for patients/caregivers, reminder systems, and better choice of injection device. The *easypod* connect system provides reminders to prompt patients to administer their treatment and allows healthcare personnel to easily monitor adherence and rapidly

Table 2. Changes in height outcomes from baseline after 1 year of *easypod* GH treatment and analysis of adherence rates with outcomes, for patients overall and by indication

Growth outcomes	Overall* (n=23)	GHD (n=17)	SGA (n=5)
Median baseline height (range), cm	136.9 (121.0-146.0)	138.0 (124.0-148.0)	127.5 (103.0-132.7)
Median baseline height SDS	-2.13 (-2.84 - -1.34)	-1.99 (-2.84 - -1.34)	-2.68 (-2.71 - -1.97)
Median change in height, cm	6.2 (3.4-8.8)	6.5 (5.6-9.0)	4.6 (3.0-7.8)
Adherence correlation (n)	0.657 (10)	0.486 (6)	0.800 (4)
P value	0.039	0.329	0.200
Median change in height SDS	0.34 (0.03-0.51)	0.34 (0.10-0.48)	-0.04 (-0.44-0.59)
Adherence correlation (n)	0.626 (10)	0.086 (6)	1.000 (4)
P value	0.053	0.872	<0.001
Median height velocity, cm/year	6.50 (4.33-9.11)	7.07 (5.96-9.11)	4.77 (3.08-7.92)
Adherence correlation (n)	0.815 (10)	0.714 (6)	1.000 (4)
P value	0.004	0.111	<0.001
Median height velocity SDS	1.43 (-0.62-3.01)	1.87 (0.04-3.06)	-0.74 (-3.40-1.48)
Adherence correlation (n)	0.340 (10)	-0.029 (6)	0.800 (4)
P value	0.336	0.957	0.200

Adherence correlations by Spearman's product-moment values (number of patients with available data). SDS=standard deviation score (*including one Turner syndrome patient who received treatment for 9.1 months).

resolve any problems. High levels of satisfaction with the device were shown in early studies of *easypod*.^{16,26} *Easypod* version 5.2 was used at the time of this study. It has been superseded by *version 6.0*, with improvements in the docking station, battery status accuracy, graphical view of adherence, caution messages, needle compatibility, and the needle release button. These improvements are considered likely to enhance ease of use and potentially increase adherence.

All subjects in the Asia-Pacific cohort were already receiving GH when they switched to using *easypod* at study entry, in contrast to other studies of only or largely GH-naïve children.^{16,17,20,22} Adherence in a 3-month study was reportedly higher in GH-naïve children than those already receiving GH,¹⁶ however, there was no apparent difference in ECOS overall between GH-naïve and already GH-treated patients.¹⁷

Adherence rate in the Asia-Pacific cohort was similar for GHD and SGA subjects, although median adherence decreased slightly between 9 months and 1 year in the SGA group. The first-year response to GH treatment is generally greater in children with GHD than those born SGA.^{27,28} In our study, the response to GH at 1 year was acceptable for GHD subjects, but SGA subjects had very little height gain and low height velocity SDS. The initial median GH dose was lower for the SGA group than the GHD group, whereas other studies indicated that a higher dose is required for SGA patients and that GH dose is the highest ranked

predictor of response.²⁷⁻³⁰ While all SGA subjects had dose adjustments, the average dose over the year may have been insufficient to promote a better response.

There was a statistically significant correlation between adherence and change in height at 1 year, supporting the clinical utility of monitoring adherence. There were also significant correlations seen in SGA subjects, whose growth response to GH was low. Good adherence was seen in these patients up to 9 months, followed by a slight decline. Thus, the results were consistent with reduced adherence resulting in decreased growth response.

The study was limited by the small sample size and short time frame of only one year, in contrast to the overall ECOS where adherence and growth outcomes using *easypod* could be assessed for up to five years in multiple patients. While the study was non-interventional, this meant that it should reflect routine clinical practice within Asia-Pacific countries. In ECOS overall, the majority of patients were Caucasian (68%), whereas children involved in this analysis were all of Asian ethnicity, which may have had an influence on the growth results. Additionally, the children were largely pubertal at the start of GH treatment, particularly for those with GHD who had a mean age of 11.6 years. Better response is seen when GH is initiated pre-pubertally.^{1,4-6,30} Thus, the full pattern of catch-up growth could not be fully assessed in this study.

In conclusion, this analysis provided real-time

adherence data for children treated with GH in routine clinical practice in Asia-Pacific countries. High adherence rates are maintained over one year after starting GH therapy with the *easypod* device. Growth response to GH is seen in GHD patients, although little response is seen in SGA patients, possibly due to an insufficient GH dose. Significant correlations between adherence to GH therapy and 1-year growth response are found. The *easypod* connect system enables physicians to easily monitor adherence and take appropriate action in order to improve growth outcomes.

Conflicts of interest

Tianrong Ma is an employee of *Merck Serono Pharmaceutical Ltd*, Beijing, China, an affiliate of *Merck KGaA*, Darmstadt, Germany. Leroy Ovbude was an employee of *Business & Decision Life Sciences (Woluwe-Saint-Lambert)*, Brussels, Belgium) at the time of the study and received related honoraria and research grants from *Merck KGaA*, Darmstadt, Germany; he is currently an employee of *GSK (Wavre, Belgium)*.

Other authors declare no conflict of interest with regard to this study.

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